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1st Congress of Fatty Liver and Metabolic Syndrome

From Basic Science to the Clinical Praxis

Budapest, 12–14 November 2009
Hotel Ramada Resort – Aquaworld Budapest
Íves út 16, H-1044 Budapest, Hungary

Our **international** meeting with leader scientists and clinicians from more than 20 countries presents the up-to-date knowledge on the study and treatment of fatty liver disease, metabolic syndrome and relating diseases, and offers the best atmosphere to discuss groundbreaking research and progressive clinical treatments.

Main topics

Molecular biology and pathophysiology of altered liver function

Clinical appearances (fatty liver, NASH, HCC)

Fatty liver disease in children

Dyslipidemia and fatty liver

Diabetes and fatty liver

Fatty liver and viral hepatitis

Recent insights and new directions in therapy

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Emil Fraenkel (Kosice)
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Program Overview

<table>
<tr><th>12 November</th><th colspan="2">13 November</th><th>14 November</th></tr>
<tr><td>Session 1 (Part 1)
09.30–10.45</td><td colspan="2">Consensus Meeting (Part 1)
08.45–10.30</td><td>Session 6
09.00–10.30</td></tr>
<tr><td>Coffee break</td><td colspan="2">Coffee break</td><td>Coffee break</td></tr>
<tr><td>Session 1 (Part 2)
11.30–13.00</td><td colspan="2">Consensus Meeting (Part 2)
11.00–12.30</td><td>Session 7
11.30–13.10</td></tr>
<tr><td>Lunch</td><td colspan="2">Lunch</td><td>Lunch</td></tr>
<tr><td>Session 2
14.00–15.10</td><td colspan="2">Session 4
14.00–15.30</td><td rowspan="7"></td></tr>
<tr><td>Coffee break</td><td colspan="2">Coffee break</td></tr>
<tr><td>Session 3
16.00–18.00</td><td colspan="2">Session 5
16.00–17.30</td></tr>
<tr><td>Concert
19.30–20.30</td><td>Poster section
17.30–18.30</td><td>COST Meeting
17.30–18.30</td></tr>
<tr><td rowspan="2">Dinner</td><td colspan="2">Concert
18.30–19.30</td></tr>
<tr><td colspan="2">Dinner</td></tr>
</table>

Venues:

Sessions: Amazonas 1
Poster section: Amazonas 4
COST Meeting: Amazonas 5

Program

12 November, Thursday

8.00-19.00 Registration

10.00-19.00 Poster viewing

SESSION 1 (Part 1): Molecular biology of lipid accumulation in the liver

Chairmen: **Mandl, J.** *(Hungary)*, **Chatgilialoglu, C.** *(Italy)*

09.30-09.50 **József Mandl** *(Hungary):* The role of endoplasmic reticulum in the metabolic syndrome *O-1*

09.50-10.10 **Chrys Chatgilialoglu** *(Italy):* Trans fatty acids in membranes: from nutrition to radical stress *O-2*

10.10-10.30 **Grzegorz Bartosz** *(Poland):* Reactive oxygen species: Destroyers or messengers in non-alcoholic fatty liver? *O-3*

10.30-10.45 **Tao Zeng,** Ke-Qin Xie *(P.R. China):* Garlic oil prevented acute ethanol-induced hepatosteatosis via inhibition of microsomal oxidases and activation of antioxidant system *O-4*

10.45-11.30 *Coffee break*

SESSION 1 (Part 2): Molecular biology of lipid accumulation in the liver

Chairmen: **Eckl, P.** *(Austria)*, **Bánhegyi, G.** *(Italy)*

11.30-11.50 **Peter Eckl,** A. Alija, W. Siems, E. Bojaxhi, C. Vogl, G. Martano, H. Stutz, N. Bresgen *(Austria)*: Toxicological properties of β-carotene in the liver *O-5*

11.50-12.10 **Miklós Csala** *(Hungary)*: Prereceptorial glucocorticoid activation: a means of nutrient sensing with implications in metabolic syndrome *O-6*

12.10-12.30 **Gábor Bánhegyi** *(Italy)*: Nonalcoholic fatty liver disease and endoplasmic reticulum redox state *O-7*

12.30-12.45 **Zemin Yao** *(Canada)* The expression of new protein factors on hepatic lipoprotein production and on the diabetic dyslipidemia and diabetic hepatosteatosis *O-8*

12.45-13.00 **Kasey C. Vickers,** A.M. Aponte, A.T. Remaley *(USA)*: A Systems Biology Approach to the Hepatic Response to Dietary Fat Reveals a Novel Mechanism of Cholesterol Regulation *O-9*

13.00-14.00 *Lunch*

SESSION 2: Molecular biology of lipid accumulation in the liver

Chairmen: **Guéraud, F.** *(France)*, **Csomos, G.** *(Germany)*

14.00-14.20 **Françoise Guéraud** *(France)*: Fate of 4-hydroxynonenal in vivo: disposition and metabolic pathways *O-10*

14.20-14.40 **Péter Fülöp** *(Hungary)*: Molecular biology of lipid accumulation in the liver *O-11*

14.40-15.00 **Martha C. Garcia,** T. J. Flynn *(USA)*: Evaluation of gender differences in response to hepatotoxicants using an in vitro fatty liver cell model *O-13*

15.00-15.10 **Paola Brun,** D.Cavallo, S. Bressan, S. Signori, S. Lancillotti, D. Martines, I. Castagliuolo *(Italy)*: Lipopolysaccharide-induced oxidative stress contributes to Hepatic Stellate Cells activation in fatty liver *O-14*

15.10-16.00 *Coffee break*

SESSION 3: Free papers

Chairmen: **Szollár, L.** *(Hungary),* **Bartosz, G.** *(Poland)*

16.00-16.25 **Guliano Ramadori,** Raddatz, D. *(Germany)*: NALFD/ NASH and hepatic control of glucose metabolism *O-15a*

16.30-16.50 **Aoun Manar,** M. Jullien, G. Fouret, F. Casas, C. Wrutniak-Cabello, MA. Carbonneau, JP. Cristol, C. Coudray, C. Feillet-Coudray *(France)*: A grape polyphenol extract reduces liver lipid content in rats fed a high fat-high sucrose diet: the SIRT1/AMPK signaling pathway *O-17*

16.50-17.00 **Wolfgang Kratzer,** Mark M. Haenle; Atilla S. Akinli; Bernhard O. Boehm *(Germany)*: Prevalence and risk factors of focal sparing in hepatic steatosis *O-18*

17.00-17.10 **Fabio Santos Lira,** A. Shimura Yamashita, D. Caetano Gonçalves, Waldecir, P. Lima, L. C. Carnevali, J. Cesar Rosa, E. Chagas Caperuto, L. F. Costa Rosa*, M. Seelaender (*Brazil*, *in memoriam): Exercise increases liver fatty acid oxidation and prevents steatosis in tumour-bearing rats *O-19*

17.10-17.20 **Mary G. Murphy,** P. D. Acott, J. Upham, J. F. S. Crocker, L. Geldenhuys, P. O'Regan *(Canada)*: Molecular mechanism of petrochemical-induced nonalcoholic fatty liver *O-20*

17.20-17.30 **Markus M. Schmid,** B. J. Connemann, R. C. Wolf, C. Eisenbach, C. Flechtenmacher, C. Schönfeldt-Lecuona *(Germany)*: Fatty degeneration and acute liver failure with valproic acid and duloxetine *O-21*

17.30-17.40 **Gaetano Serviddio,** F. Bellanti, A.D. Romano, R. Tamborra, T. Rollo, M. Blonda, D. Bruno, G. Vendemiale, E. Altomare *(Italy)*: Oxidative stress, mitochondrial dysfunction are associated with the opening of permeability transition pore in a rodent model of NAFLD *O-22*

17.40-17.50 **Renata Silverio** *(Brazil)*: L-carnitine counteracts cancer cachexia- associated steatosis in rats *O-23*

17.50-18.00 **S. Zucoloto**, G.R. Oliveira, A.K. Sankarankutty, O. Castro e Silva, J. Ferreira, C. Kurachi, H. Vannuchi, A.A. Jordão Jr., J.S. Marchini and V.S. Bagnato *(Brazil)*: Fluorescence spectroscopy to diagnoses hepatic steatosis in a rat model of fatty liver *O-24*

19.30-20.30 *Concert*

20.30 *Dinner*

13 November, Friday

08.00-19.00 Registration

09.00-19.00 Poster viewing

CONSENSUS MEETING (Part 1): Consensus/Index for Fatty Liver

Moderator: **Fehér, J.** *(Hungary)*

The purpose of his presentation is to create a platform to come up with an International Consensus on how to indicate Non-Alcoholic Fatty Liver Disease.

08.45-09.05 **K. T. Shenoy** *(India)*: The need for an international NAFLD-Index *O-25*

09.05-09.30 **H. Hesham A-Kader,** M. D. Merrell, A. J. Lickteig, C. D. Fisher, L. M. Augustine, S. B. Campion, J. E. Manautou, R. P. Erickson, N. J. Cherrington *(USA)*: Acetaminophen disposition: A novel metabolomic biomarker for non-alcoholic fatty liver disease *O-27*

09.30-09.45 **Gábor Firneisz,** T. Varga, A. Somogyi, D. Ghyczy, L. Selmeci, J. Fehér, Zs. Tulassay, G. Lengyel *(Hungary)*: Higher serum dipeptidyl peptidase-4 activity and insulin resistance index in non-alcoholic fatty liver disease in patients with similar degree of obesity *O-28*

09.45-09.55 **Emil Fraenkel,** Gy. Szabó, P. Jarčuška, G. Lengyel, J. Fehér *(Hungary)*: Does the carbohydrate deficient transferrin have a diagnostic value in non alcoholic fatty liver? *O-29*

09.55-10.05 **Theresa C. Peterson,** S. Caldwell, K.M. Peltekian, M.R. Peterson *(Canada)*: Utility of FSI in documenting fibrosis in NASH *O-30*

10.05-10.15 **Abdulwahhab Al-Isa** *(Kuwait)*: Using Two Criteria to Assess the Prevalence of Metabolic Syndrome (MS) among Male Kuwaiti Adolescents *O-31*

10.15-10.30 **Ágnes Szebeni,** László Halmy *(Hungary)*: Ultrasound in the diagnostic of fatty liver in obesity *O-32*

10.30-11.00 *Coffee break*

11.00-12.30: CONSENSUS MEETING (Part 2): Multifactorial treatment of fatty liver diseases. Metadoxine in fatty liver diseases – Round Table Conference

Moderator: **Fehér, J.** *(Hungary)*

János Fehér *(Hungary)*: Introductory remarks: Therapy modalities in non-alcoholic steatohepatitis *O-33*

Wattana Sukeepaisarnjaroen *(Thailand)*: Multifactorial pathogenesis of the liver alterations in NAFLD and NASH

János Fehér *(Hungary)*: Multifactorial mechanism of action of Metadoxine *O-33*

L. Miele *(Italy)*: Overview of clinical studies performed on Metadoxine

K. T. Shenoy *(India)*: Clinical experience with Metadoxine in NAFLD and NASH

E. R. Parise *(Brazil)*: Clinical data on the use of Metadoxine in NAFLD

T. Abel *(Hungary)*: NAFLD the silent killer in the metabolic syndrome, role of Metadoxine

Discussion, Conclusions

12.30-14.00 *Lunch*

SESSION 4: Pathology – pathophysiology

Chairmen: **Zarkovic, N.** *(Croatia)*, **Poli, G.** *(Italy)*

14.00-14.20 **Lajos Szollár** *(Hungary)*: Metabolic Syndrome – a Ghost with Real Weapons? *O-34*

14.20-14.40 **Neven Zarkovic** *(Croatia)*: The relevance of lipid peroxidation in liver pathopysiology *O-35*

14.40-15.00 **Giuseppe Poli** *(Italy)*: Lipid oxidation, inflammation and fibrosis *O-36*

15.00-15.15 **Gyorgy Trencsenyi** *(Hungary)*: Comparison of tumorogenicity of liver and kidney tumors induced by N-nitrosodimethylamine in rats *O-37*

15.15-15.30 **Kamal D. Mehta:** Protein kinase C beta (PKCbeta) plays an important role in regulating whole-body's triglyceride homeostasis *O-38*

15.30-16.00 *Coffee break*

SESSION 5: Clinical forms (fatty liver, NASH, HCC)

Chairmen: **Biasi, F.** *(Italy)*, **Halmy, L.** *(Hungary)*

16.00-16.20 **Fiorella Biasi** *(Italy)*: Lipid oxidation and fibrogenesis in cancer progression *O-39*

16.20-16.35 **László Halmy** *(Hungary)*: Obesity and fatty liver *O-40*

16.35-16.50 **György Paragh,** P. Fülöp *(Hungary)*: The effect of statins on the hepatocyte function *O-41*

16.50-17.05 **Tatjana Ábel** *(Hungary)*: Statins in the therapy of fatty liver *O-42*

17.05-17.25 **Giuseppe Carruba** *(Italy)*: Estrogen receptor variants may be implicated in carcinogenesis and progression of human hepatocellular carcinoma *O-43*

17.30-18.30 **Closed COST B35 Meeting**

Chairman: **Neven Zarkovic**

17.30-18.30 **Poster Section**

List of accepted poster presentations can be found after the program.

18.30-19.30 *Concert*

19.30 *Dinner*

14 November, Saturday

08.30-13.00 Registration

SESSION 6: Fatty liver and viral (HBV, HCV) infection

Chairmen: **Schuster, C.** *(France)*, **Pár**, **A**. *(Hungary)*

09.00-09.20 **Catherine Schuster,** T. Baumert *(France)*: Hepatitis C virus infection and lipid metabolism *O-44*

09.30-09.42 **Gabriella Lengyel** *(Hungary)*: Fatty liver and respond to combined peginterferon and ribavirin treatment *O-46*

09.42-09.55 **Alajos Pár,** Rőth, E., Miseta, A., Hegedüs, G., Pár, G., Hunyady, B., Voncze, Á. *(Hungary)* Oxidative stress and antioxidant therapy in chronic viral hepatitis *O-46.a*

09.55-10.10 **Béla Lombay,** F. Szalay *(Hungary)*: The negative role of insulin resistance for sustained virological response in chronic hepatitis C patients *O-47*

10.10-10.25 **János Osztovits,** T. Horváth, E. Horváth, L. Csihi, J. Tax, G. Bekő, T. Tóth, M. Abonyi, M. Kollai, P. Kempler, J. Fehér, H. E. Blum, F. Szalay *(Hungary)*: Autonomic and sensory nerve functions during 48 weeks of anti-HCV treatment. A follow-up study *O-48*

10.30-11.30 *Coffee break*

SESSION 7: Free papers

Chairmen: **Ramadori, G.** *(Germany),* **Carruba, G.** *(Italy)*

11.30-11.40 **Brun Paola,** D. Cavallo, S. Dagnolo, S. Signori, D. Martines, I. Castagliuolo *(Italy)*: Mice carrying a Toll-like receptor 2 mutation on high fat diet show increased accumulation of body fat albeit attenuation of insulin resistance *O-49*

11.40-11.50 **Matthias Heuer,** A. Paul, G. M. Kaiser, Z. Mathé, S. Vernadakis, J. P. Neuhaus, F. H. Saner, A. Canbay, J. W. Treckmann *(Germany)*: Nonalcoholic steatohepatitis and liver transplantation experience of the University Hospital of Essen *O-50*

11.50-12.00 **Aoun Manar,** G. Fouret, F. Michel, JP. Cristol, C. Coudray, MA. Carbonneau, C. Feillet-Coudray *(France)*: Polyphenols partially prevent hepatic steatosis and modulate liver fatty acid composition in rats fed a high fat-high sucrose diet *O-51*

12.00-12.10 **Gar-Yang Chau,** Shyh-Haw Tsay *(Taiwan)*: Evaluation of age-related, different clinicopathological features of patients with resectable hepatocellular carcinoma *O-52*

12.10-12.20 **Diana Christina Goncalves**, FS. Lira, AS. Yamashita, LC. Carnevali Jr., R. Eder, WP. Lima, M.C.L. Seelaender *(Brazil)*: Conjugated linoleic acid (CLA) fails to reduce steatosis in cachectic tumor-bearing rats *O-53*

12.20-12.30 **Raoul Saggini,** R. G. Bellomo, M. Calvani, R. Calvani *(Italy)*: Personalized rehabilitation approach to Fatty Liver Disease in patients with metabolic syndrome *O-54*

12.30-12.40 **Olha Yelisyeyeva**, A.P. Cherkas, K.H. Semen, V. Serhiyenko, O. Serhiyenko *(Ukraine)*: The efficiency of Amaranth oil for correction of oxidative stress and improvement of heart rate variability in patients with type 2 Diabetes mellitus *O-55*

12.40-12.50 **Güngör Kanbak** *(Turkey)*: Alcohol toxicity and fatty liver preventive effects of betaine and s-adenosyl methionine *O-56*

12.50-13.00 **Majid Hajifaraji,** Haddad-Tabrizi Sara, Husain-Panah Farhad, Houshyar-rad Anahita, Abadi Alireza *(Iran)* The Association of Metabolic Syndrome and Food Pattern In Non-Menopause Women *O-57*

13.00-13.10 **Tamas Szamosi,** Tamas Kalovics, Tamas Szamosi Jr, Antal Czinner, Zoltan Harkanyi, Zoltan Karadi, Erika Tomsits *(Hungary):* Life modification treatment of NAFLD in schoolchildren *O-58*

13.10 *Closing remarks*

13.30-14.30 *Lunch*

Poster presentations

P-1

Baginskaya NV[1], Ilnitskaya CI[1], Perepechaeva ML[2], Pivovarova EN[1], Kaledin VI[1] ([1]Institute of Cytology and Genetics SB RAS, Russia, [2]Institute of molecular biology and biophysics SB RAMS, Russia): **Induction of fatty liver by fasting in mouse strain disposed to metabolic syndrome development**

P-2

Ilaria B, Cavallo MG, Angelico F, Del Ben M, Fraioli A, Morini S, Pozzilli P (IV Division of Internal Medicine, Policlinico Umberto 1, Rome, Italy) **Association between vitamin D, cardiovascular risk factors and non-alcoholic fatty liver disease (NAFLD) in Italian patients with the metabolic syndrome**

P-3

Kasapoglu B (Endocrinology Department, Fatih University Hospital, Turkey) **Does the chronic intermittant hypoxia link between obstructive sleep apnea and fetty liver disease?**

P-4

Décordé K[1], Agne A[1], Lacan D[2], Ramos J[3], Fouret G[4], Ventura E[1], Feillet-Coudray C[4], Cristol JP[1], Rouanet JM[1] ([1]UMR prevention of Malnutritions and Linked Pathologies, University of Montpellier, [2]Bionov Sarl, Agroparc Site, Avignon, [3]Pathologic Anatomy Laboratory, Hospital Universitary Center Gui de Chauliac, Montpellier, [4]UMR 866 Cellular Differenciation & Growth, INRA, Montpellier, France): **Preventive effect of a melon extract rich in superoxide scavenging activity on obesity, oxidative stress and non alcoholic steatohepatitis in hamsters fed a high fat diet.**

P-5

Forni GL[1], Villa R[1], Carrara P[1], Trabacca MS[2], Balocco M[1] ([1]Centro della Microcitemia e delle Anemie Congenite, E.O. Ospedali Galliera di Genova, [2]S.C. Medicina Interna, E.O. Ospedali Galliera di Genova, Genova, Italy): **Liver iron overload in patients with unexplained hyperferritinemia, Impaired Fasting Glucose and liver steatosis**

P-6

Fajfrová J[1], Šafka V[2,3], Pavlík V[1], Hlúbik P[1] ([1]Dept. of Military Hygiene, Faculty of Military Health Science University of Defence, [2]Dept. of Physiology Charles University – Faculty of Medicine in Hradec Králové, [3]2nd Dept. of Medicine University Hospital, Hradec Králové, Czech Republic): **The relationship between metabolic syndrome components and increased alanine aminotransferase activity**

P-7

Ábel T, Wimmer A, Lengyel G, Eldin MG, Kovács A, Feher J. (Outpatient Clinic, National Health Centre, 2nd Department of Internal Medicine, Medical Faculty, Semmelweis University, Budaörs Health Centre, Med Medical Service-providing Ltd. Hungary): **The moderate white wine consumption and the insulin resistance**

P-8

Lin YC, Hsiao TJ, Chen PC (Department of Family Medicine, Tao-Yuan General Hospital, Tao-Yuan; School of Medicine, Fu Jen Catholic University; Institute of Occupational Medicine and Industrial Hygiene, College of Public Health, National Taiwan University, Taipei, Taiwan): **Fatty liver and elevated blood pressure contribute synergistically to the development of metabolic syndrome among non-obese adults**

P-9

Garnol T, Kučera O, Křiváková, P, Lotková H, Roušar T, Červinková Z (Dept. of Physiology, Charles University in Prague, Faculty of Medicine in Hradec Králové, Hradec Králové, Czech

Republic): **Liver regeneration after partial hepatectomy in the liver affected by non-alcoholic fattyliver diseae**

P-10

Hegedűs V, Mihály Z, Sárdi É, Szentmihályi K, Blázovics A (2nd Department of Internal Medcine, Semmelweis Univeristy, Budapest, Hungary): **Molecular biological changes in alimentary induced fatty liver**

P-11

Babaei H, Sadeghzadeh M, Khoshnevisasl P, Kavandi S (Paediatrics Ward, Mousavi Hospital, Zanjan University of Medical Sciences, Zanjan, Iran): **A female child involved type 1 Crigler-Najjar syndrome**

P-12

Nishino H (Ritsumeikan University, Kyoto, Japan): **Prevention of viral-induced liver cancer by myo-inositol, one of the anti-fatty liver food factors**

P-13

Lee JG, Min HG, Lee S, Kim JY (Center for Obesity, Nutrition and Metabolism, Department of Family Medicine, Pusan National University Hospital, Busan, South Korea): **The association of obesity with elevated alanine aminotransferase**

P-14

Piao LS, Hur W, Choi JE, Hong SW, Lyoo KS, Yoon SK (Department of Internal Medicine & WHO Collaborating Center of Viral Hepatitis, The Catholic University of Korea, Seoul, Korea): **Establishment of *in vitro* model system of hepatic steatosis using hepatocyte**

P-15

Özlem Kar[1], Remise Gelisgen[2], Füsun Erdenen[1], Esma Altunoğlu[1], Taşkın Rakıcı[3], Yüksel Barut[3], Abdullah Yüksel[1], Hafize Uzun[2], Hale Aral[4], Güvenç Güvenen[4] (Ministry of Health Istanbul Education and Research Hospital, [1]Internal Medicine Clinics, [3]Radiology Department, [4]Central Clinical Chemistry Laboratory, Istanbul; [2]Istanbul University Cerrahpasa Medical School, Biochemistry Department, Istanbul, Turkey): **Comparison of serum anticardiolipin antibodies and carotid intima media thickness in diabetic patients**

P-16

Krawczykowsky D[1], Karcz WK[2] ([1]Polyclinique Priollet/Courlancy Chalons en Champagne France, [2]Clinics of Surgery Division of Bariatric and Metabolic Surgery, Freiburg, Germany): **Liver histopathology by 100 patients with diabetes type II underwent LSG surgery**

P-17

Krawczykowski D, Melin P, Nduwayo L, Karcz WK (Polyclinique Priollet/Courlancy Chalons en Champagne France, Centre hospitalier de Saint Dizier France, Clinics of Surgery Division of bariatric and metabolic surgery Freiburg Germany): **Liver biopsy in morbidly obese patients**

P-18

Kjaer MA, Vegusdal A, Berge GM, Galloway TF, Hillestad M, Krogdahl Å, Holm H, Ruyter B (Nofima - The Norwegian Institute of Food, Fisheries and Aquaculture, Ås, Norway): **Characterization of lipid transport in Atlantic cod liver when fasted and fed high or low fat diets**

P-19

Kosenko EA, Kaminsky YG, Montoliu C (Institute of Theoretical and Experimental Biophysics, Pushchino State University, Puschino, Russia, Fundación Investigación Hospital Clínico Universitario de Valencia,

Spain): **AMP deaminase and adenosine deaminase are activated in ammonia intoxication and hepatitis**

P-20

Kucera O, Krivakova P, Lotkova H, Rousar T, Garnol T, Cervinkova Z (Department of Physiology, Charles University in Prague, Faculty of Medicine in Hradec Kralove, Czech Republic): **Is the rat liver affected by non-alcoholic steatosis more susceptible to toxic effect of thioacetamide?**

P-21

Hagymási K, Mihácsi G, Mezei M, Fehér J, Lengyel G (2nd Dept. of Internal Medicine, Semmelweis University, Budapest, Hungary): **Determination of severity of hepatic steatosis in chronic hepatitis C by computer-assisted morphometric image analysis-correlation with clinical data and treatment response**

P-22

Martín-Castillo A[1], Castells M[2], García-Pérez B[3], Sánchez-Polo M[3], Adanez G[3], Ayala I[4], Montes A[4] ([1]Department of Medicine, División of Gastroenterology, Santa María del Rosell University Hospital, Cartagena. Murcia, [2]Department of Cell Biology, University of Murcia, [3]Internal Medicine Service, Virgen de la Arrixaca University Hospital. Murcia, [4]Department of Animal Medicine and Surgery, Veterinary Faculty, University of Murcia, Spain.): **Effects of atorvastatin on progression-regression of steatohepatitis in hyperlipidemic chickens**

P-23

Chang ML, Yeh CT, Chiu CT, Lin DY (Liver Research Unit, Department of Hepatogastroenterology, Chang Gung Memorial Hospital, Taoyuan, Taiwan): **Steatohepatitis mediated by hepatitis C virus core protein is ameliorated by blocking complement activation**

P-24

Mohammed Ibrahim (Dept of Medicinal chemistry / Pharmacology / Nizams group of Institutions, Andhra Pradesh, India): **Curative effect of extracts of *Sapindus mukorossi* and *Rheum emodi* in CCl4 induced liver cirrhosis in male rats**

P-25

Molnár L, Noetel A, Rey J, Sandelin B, Scheffler M, Kasper HU, Gerken G, Canbay A, Dienes HP, Odenthal M (Institut für Pathologie, Unversität Köln, Germany): **Genetic polymorphisms of the Peroxisome proliferator-activated receptor γ (PPAR γ) and Leptin receptor gene in patients with Non-Alcoholic Fatty Liver Disease (NAFLD)**

P-26

Rosa J, Sinđić A, Jakovac D, Rosa J (Department of Physiology School of Dentistry, Department of Physiology School of Medicine, University of Zagreb, Croatia): **Metabolic changes in hepatocytes from rats on raw soybean diet**

P-27

Setyowati KD[1], Arunmozhiarasi A[1], Tavintharan S[2], Michael W[3], Chun TE[3], Chi LS[2], Fang SC[2], Kandiah J[1] ([1]Department of Biochemistry, Yong Loo Lin School of Medicine, National, University of Singapore, [2]Department of Medicine, Alexandra Hospital, Singapore, [3]Health For Life Centre, Alexandra Hospital): **MicroRNAs: Potential therapeutic targets for metabolic syndrome, a predictor of fatty liver**

P-28

Sugiyama S, Nakaguchi T, Yamamoto S, Namiki T, Tsumura N, Miyake Y (Graduate School of Advanced Integration Science, Chiba University, Japan): **Quantitative diagnostic system for abdominal palpation**

P-29

Vlasov S[2], Zoloedov VI[1], Miroshnichenko LA[2], Volyinkina AP[1], Gorshkov IP ([1]Voronezh State Medical Academy named after Burdenko, [2]LLC "Russian Olive", Voronezh, Russia): **Amaranth oil impact on improvement of metabolic parameters in adult patients with diabetes type 2**

P-30

Hafize U[1], Erman A[2], Gulgun T[3], Veysel T[4,5], Remise G[1], Omur T[6], Erol A[4] ([1]Department of Biochemistry, [2]Department of General Surgery, Istanbul University Cerrahpasa Medical Faculty, [3]General Surgery Unit, Institute of Gastroenterology, Marmara University, Istanbul, [4]Institute of Gastroenterology, Marmara University, Istanbul, [5]Department of Human Researches, University of Pittsburgh, PA, USA, [6]Department of Internal Medicine, Istanbul Education and Research Hospital, Istanbul, Turkey): **Melatonin prevents oxidative DNA damage in non-alcoholic steatohepatitis: an experimental study**

P-31

Vaško L[1], Kubálková J[1], Kaštel' R[2] ([1]Department of Medical Chemistry, Biochemistry and Clinical Biochemistry, Faculty of Medicine, Pavol Jozef Šafárik University in Košice, [2]Institute of Pharmaceutical and Medical Chemistry, University of Veterinary medicine, Košice, Slovak Republik): **Primary human omega-6 and omega-3 ratio intake improvement by animal dietary adjustment**

P-32

Meisheng W, Haihong C, Xia C, Yifeng T (Institute of Analytical Chemistry, Department of Chemistry, Suzhou University, Suzhou, China): **A nano-functionalized real-time electrochemiluminescent biosensor for alanine transaminase assay**

P-33

Han Z (School of Chemical Engineering, Huaihai Institute of Technology, Lianyungang, Jiangsu, China): **Effects of PFOs on Carassius Aurats and kinetics models**

P-34

Yamaguchi T. (Research Center for Frontier Medical Engineering, Chiba University, Chiba, Japan): **Quantitative evaluation method of diffuse liver diseases based on characteristics analysis of echo signal**

P-35

Baginskaya N. (Institute of Cytology and Genetics, Siberian Branch of Russian Academy of Sciences, Russia): **Details of special diets and additional information**

P-36

Ghareeb DA[1], Khalil AA[2], Hafez H[3], Salem MA[4], Mansour NF[5] ([1]Department of Biochemistry, Faculty of Science, Alexandria University, [2]Department of Protein Technology, Institute of Genetic Engineering and Biotechnology, Mubarak City for Scientific Research, New Borg Elarab, [3]Department of Zoologyt, Faculty of Science, Cairo University, [4]Department of Pathology, Faculty of Medicine, Alexandria University, [5]Faculty of Pharmacy, Alexandria University, Alexandria, Egypt): **From steatosis to steatohepatitis: is there any early diagnostic marker?**

P-37

Ovcharenko NA, Reshetnikova OS, Zinchenko OV, Pinskyy LL (Lugansk State Medical University, Lugansk, Ukraine): **Morphological features of adjournment lipid granules at patients with chronic hepatitis C and opioid drug addiction**

P-38

Ming-Hua Zheng, Ke-Qing Shi, Bi-Hong Zhu, Yong-Ping Chen (Department of Infection and Liver Diseases, The First Affiliated Hospital of Wenzhou Medical College, Wenzhou, China): **Profiles of ALT in male subjects with sonographic fatty liver carrying serum HBsAg**

P-39

Ming-Hua Zheng[1], Yong-Ning Xin[2], Ke-Qing Shi[1], Yong-Ping Chen[1] ([1]Department of Infection and Liver Diseases, The First Affiliated Hospital of Wenzhou Medical College, Wenzhou, China, [2]Department of Liver Diseases, Qingdao Municipal Hospital, Qingdao, Shandong Province, China): **Aquaporin, a kind of membrane channel protein, maybe a new promising therapeutic target for non-alcoholic fatty liver disease**

P-40

BC Sharma, A Kumar, P Sakhuja, SK Sarin (Department of Gastroenterology and Pathology, G B Pant Hospital New Delhi, India): **Efficacy of pentoxifylline versus pioglitazone intreatment of non alcoholic steatohepatitis**

Oral Presentations

O-1
The role of endoplasmic reticulum in the metabolic syndrome

Mandl J
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O-2
Trans fatty acids in membranes: from nutrition to radical stress

Chatgilialoglu C
ISOF - Consiglio Nazionale delle Ricerche (CNR), Bologna, Italy

O-3
Reactive oxygen species: Destroyers or messengers in non-alcoholic fatty liver?

Bartosz G
Department of Molecular Biophysics, University of Lodz, Poland

O-4
Garlic oil prevented acute ethanol-induced hepatosteatosis via inhibition of microsomal oxidases and activation of antioxidant system

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Acute alcoholic fatty liver was induced by single dose of ethanol and was used to assess the protective effects of garlic oil (GO). Kun-Ming mice were pretreated with GO (50, 100, 200 mg/kg BW) or corn oil for consec-

utive 7 days before exposure to ethanol (4.8 g/kg BW). The liver index (ratio of the liver weight to body weight), liver triglycerides (TG) levels, and histological changes were examined for the fat accumulation evaluation. The activities and protein expressions of CYP2E1, 1A2, 3A, and the antioxidant system in the liver and mitochondria were determined for mechanisms exploration. GO significantly suppressed acute ethanol-induced hepatosteatosis, shown as the attenuation of the elevation of the liver index and liver TG levels. Compared with that of ethanol group, the liver TG levels were decreased by 32.90%, 33.50%, and 47.57%, respectively ($P<0.01$), in three doses of GO groups. Histological examination showed fewer droplets in the GO-pretreated mice liver. Besides, the liver and mitochondrial malondiadehye (MDA) contents were significantly increased by ethanol treatment, which were concurrently attenuated by GO pretreatment. In addition, GO markedly inhibited the CYP2E1, slightly suppressed CYP1A2, but did not influence CYP3A. Moreover, the liver and mitochondrial glutathione contents were significantly increased and the antioxidant enzymes were differently enhanced in GO-pretreated mice. These data indicated that the hepatoprotective effects of GO against ethanol might be associated with the activation of the antioxidant system and the suppression of the microsomal ethanol oxidizing system. The CYP2E1 and 1A2 inhibition reduced the production of reactive oxygen species (ROS), while the activation of the antioxidant system accelerated the elimination of the ROS. These two factors may work synergistically and contribute to the attenuation of the oxidative stress, which account for the protection of GO against acute ethanol exposure.

O-5
Toxicological properties of β-carotene in the liver

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β-Carotene is a fat-soluble pigment found in plants, where it serves as an accessory light-gathering pigment and to protect from toxic effects of oxygen. It is stored in the liver and converted to vitamin A. Apart from its action as provitamin, β-carotene has been demonstrated to have antioxidant activity *in vitro* i.e. by scavenging peroxyl radicals and inhibiting lipid peroxidation. Since many diseases, such as cancer, cardiovascular and neurodegenerative diseases, are associated with oxidative stress, the antioxidant properties of carotenoids, especially of β-carotene, are widely used as a strategy to prevent their development. However, the Alpha-Tocopherol Beta-Carotene Cancer Prevention Study and the Beta-Carotene and Retinol Efficacy Trial unexpectedly showed an increased risk of lung cancer in smokers, which can be explained by the formation of cleavage products formed by free radical attack. In fact, chemical analysis of β-carotene degraded by hypochlorite treatment revealed a large variety of breakdown products. Since it has further been shown that β-carotene supplementation results in the over-generation of oxygen radicals, particularly in the liver, and that alcohol consumption in combination with β-carotene results in hepatoxicity, both a mixture of cleavage products obtained by hypochlorite bleaching of β-carotene and apo8`-carotenal were tested in primary hepatocyte cultures and resulted in a genotoxic potential of CP and apo8` at concentrations as low as 100 nM. In order to simulate conditions leading to the formation of oxidative cleavage products in vitro the cultures were treated in subsequent experiments with either dimethoxynaphthoquinone or subjected to hypoxia/reoxygenation in the presence of β-carotene. Under these conditions genotoxic effects are observed at micromolar β-carotene concentrations. In parallel cleavage products such as apo-carotenals are formed (supported by grant P20096 of the Austrian Science Foundation and COST action B35).

O-6
Prereceptorial glucocorticoid activation: a means of nutrient sensing with implications in metabolic syndrome

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O-7

Nonalcoholic fatty liver disease and endoplasmic reticulum redox state

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O-8

The expression of new protein factors on hepatic lipoprotein production and on the diabetic dyslipidemia and diabetic hepatosteatosis

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O-9

A systems biology approach to the hepatic response to dietary fat reveals a novel mechanism of cholesterol regulation

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Dietary fat has been shown to cause substantial changes in liver physiology and integrity. The typical Western diet is generally high in saturated fat; which accumulates in the liver and results in profound changes in gene regulation and metabolism. Methods & Results: C57BL6 mice were fed a high fat diet or normal chow for 3 weeks. The complete microRNA (miRNA) and mRNA gene expression profiles were determined by LC Sciences microfluidics and Affymetrix microarrays, respectively; and were validated by real-time PCR. We observed significant differential expression of 12 miRNAs and 89 mRNAs. 2D-DIGE electrophoresis and

Tandem Mass Tag Spectrometry were used to profile differential protein expression, and 84 (2D) / 131 (TMT) unique and differentially abundant proteins were identified by these techniques. Furthermore, we observed numerous changes in the metabolome as a consequence of dietary fat, as determined by GC-MS. Pathway level analysis of gene expression (PLAGE) indentified the sterol biosynthetic pathway as being one of the most active pathways in response to dietary fat. A majority of the top most down-regulated mRNAs are essential components (enzymes) within the cholesterol biosynthesis pathway (14/16). Six of these 14 altered mRNAs are the direct targets of our top most up-regulated miRNAs. We experimentally validated the targeting of these predictions biochemically, using synthetic miRNAs. Mmu-mir-690,699,710 and 329 have all been confirmed to significantly knockdown multiple enzymes (mRNA) in the cholesterol biosynthesis pathway with resulting precursor metabolite accumulation. In addition to identifying a novel mechanism for cholesterol regulation, we have used these organized data sets (systems biology) to develop and test new hypotheses related to amino acid metabolism and Smith-Lemli Opitz Syndrome. Conclusion: In summary, we have used a systems biology approach to explore previously unknown relationships involved in the intricate hepatic response to dietary fat. The integration and organization of multiple datasets, utilizing conceptualization programs, proved invaluable in observing novel mechanisms of fat-sensing and gene regulatory responses with metabolic outcomes.

O-10

Fate of 4-hydroxynonenal in vivo: disposition and metabolic pathways

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O-11

Molecular biology of lipid accumulation in the liver

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O-12
Peroxisome proliferator-activated receptors in liver pathophysiology

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O-13
Evaluation of gender differences in response to hepatotoxicants using an in vitro fatty liver cell model

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Nonalcoholic fatty liver disease (NAFLD) is an increasingly recognized cause of chronic liver disease worldwide and is often associated with obesity and diabetes. While some reports indicate the incidence of nonalcoholic fatty liver disease affects both genders equally, others suggest that more women than men are affected by the disease. Recent studies have also shown that women are more susceptible than men to drug-induced acute liver failure. The present study explores the possible gender differences in the response to hepatotoxicants using a human hepatocellular in vitro model of fatty liver disease. Elevated serum free fatty acids and hepatocyte lipotoxicity are features of fatty liver disease that can be studied in a cellular model. This was accomplished by culturing C3A/HepG2 human hepatoma cells in medium supplemented with excess amounts of oleic acid. Using this approach, we have observed decreases in the cellular content of the antioxidant glutathione (GSH) using a luminescence-based assay. The potential for gender specific differences in the fatty liver model in response to chemical-induced toxicity will be studied using cells grown in medium containing added sex steroid hormones to mimic either the male or female profile of serum hormone concentrations.

O-14

Lipopolysaccharide-induced oxidative stress contributes to Hepatic Stellate Cells activation in fatty liver

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Generation of reactive oxygen species (ROS) is involved in the progression of fatty liver to non-alcoholic steatohepatitis (NASH). We have previously shown that in animal models of obesity, fatty liver is exposed to increased load of intestinal lipopolysaccharide (LPS). Since LPS causes respiratory burst and energy impair, in this study we aim to: 1) evaluate the role of LPS-induced ROS generation in hepatic stellate cells (HSCs) activation and viability; 2) assess the effects of LPS-induced oxidative stress on mitochondrial machinery in fatty liver. Murine HSCs (from lean and diet-induced obese C57Bl/6 mice) were exposed to LPS (10 μg/ml) with or without pre-treatment with anti-oxidant agents. ROS production was determined by fluorimetric analysis. Mitochondrial DNA (mtDNA) damage and biogenesis were assessed by qPCR on total RNA obtained from cultured HSCs, animal and human hepatic samples. Inflammatory and fibrogenic phenotype were evaluated by ELISA in conditioned medium and [3H]proline incorporation, respectively. HSCs exposed to LPS for 8 hours showed increased ROS production and reduction of NADH dehydrogenase complex I and IV mRNA levels ($p<0.05$). HSCs pre-treatment with antioxidants significantly prevented LPS-induced mtDNA damage and blunted inflammatory cytokines (IL6, IL1β) release and collagen production ($p<0.05$). LPS-induced mitochondrial damage was more evident in HSCs isolated from obese than lean mice ($p<0.05$). Moreover mtDNA deletions were significantly increased in the liver of obese animals and patients as compared to lean subjects. Although LPS stimulation induced a loss of 12% in cell viability, HSCs overcame LPS-induced insult up-regulating genes involved in mitochondrial damage recovery (Tfam and nuclear respiratory factors). Our data demonstrate that LPS-induced ROS generation is involved in HSCs activation. Thus in

fatty liver intestinal derived LPS amplifies the oxidative stress resulting in a more evident activation of HSCs.

O-15
Characteristics of Patients with NAFLD in Bangladesh

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Background: Patients with non-alcoholic fatty liver disease (NAFLD) can proceed to develop non-alcoholic steatohepatitis (NASH); and it is these patients with NASH who are at risk of developing cirrhosis of liver. Some of them even go on to develop hepatocellular carcinoma (HCC). The aim of this study was to study the profile of NAFLD patients in Bangladesh. Methods: 52 patients with non-alcoholic fatty liver disease (NAFLD) were included in the study. Of them 59.6% were males and the rest 40.4% were females. Patients were between 12-60 years of age. They presented either with dull right upper abdominal ache and/or incidental detection of raised serum transaminases and/or fatty liver on routine ultrasonography. All patients tested negative for hepatitis B and C viruses and none had any history of alcohol intake. All patients underwent per-cutaneous liver biopsy for histopathology to exclude NASH. The patients were also tested for diabetes mellitus, dyslipidaemia, insulin resistance, hypothyroidism and hepatitis C virus infection. Their body mass index (BMI) was calculated and blood pressure recorded. Results: 88.5% patients had NASH. 63.0% of them were males and the rest 37.0% females. 11.5% patients included in the study had non-alcoholic fatty liver (NAFL). Of them 50% each was males and females, respectively. Majority of the patients included in the study had NASH. 47.8% patients were obese and 41.3% had dyslipidaemia. 28.3% had hypertension, 28.3% also had insulin resistance and 13% were diabetics. 6.5% had hypothyroidism. None had chronic hepatitis C. Serum ALT was raised in 72% and normal in 28% patients respectively. On the other hand serum AST was normal and elevated in 60% and 40% respectively. Although all patients with NAFLD with fibrosis did not have elevated serum ALT level, it was raised in majority of them, contrary to serum AST values, which was normal in

most. Conclusion: This study shows that majority of NASH patients in Bangladesh are obese. Other leading causes of NASH in our population include dyslipidaemia followed by hypertension and insulin resistance. Some NASH patients also had diabetes and hypothyroidism. This study also reveals that elevated serum ALT in patients with NAFLD is suggestive of fibrosis, although normal serum ALT does not exclude NASH. The study further suggests that serum ALT is much superior to serum AST in predicting fibrosis in NAFLD patients.

O-15a
NALFD/NASH and hepatic control of glucose metabolism

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The liver plays a unique role in controlling carbohydrate metabolism by maintaining glucose concentrations in a normal range. This is achieved by a tightly regulated system of enzymes and kinases regulating either glucose breakdown or synthesis in hepatocytes. This process is under the control of glucoregulatory mediators among which insulin plays a key role. The fact that insulin is secreted into the portal system, taking the same route as absorbed glucose and that the liver eliminates a large portion of the portal insulin a the first pass highlights the role of the liver not only as glucose supply, but also as site of glucose uptake and storage. The most prevalent liver disease in developed countries is nonalcoholic fatty liver disease (NALFD). This can be associated with hepatocyte injury and inflammation that results in hepatic fibrosis and ultimately in cirrhosis. This process is described as nonalcoholic steatohepatitis (NASH). It is estimated that up to one third of adult Americans may have NALFD, whereas the prevalence of NASH is estimated 2-3 %. However, NASH is considered the most common cause of cryptogenic cirrhosis. It has been shown that glucose disposal is reduced to appr. 50% in non-diabetic NAFLD patients compared to normal subjects – a similar extent as in patients with diabetes mellitus type 2. If insulin resistance causes NALFD or vice versa, or if both conditions occur in parallel is still not completely understood. Also the matter of whether hepatic or peripheral IR have the

primacy in NALFD is still a matter of debate. In hepatocytes, the insulin resistant state is the result of most likely a combination of the following pathological alterations: hyperglycaemia and hyperinsulinaemia, formation of advanced glycation end-products (AGS), increased free fatty acids and their metabolites, oxidative stress and altered profiles of adipocytokines. However, factors that predispose simple NALFD to finally end up in NASH are not well defined yet. Clinically, an estimate of prognosis might be made by liver biopsy. Several studies on non-invasive parameters to detect liver fibrosis have recently been published, however, none of them allowed an estimate of prognosis in terms of survival or end-stage liver disease. Insulin-resistance is a target for specific treatment of NAFLD, and insulin-sensitizing agents like metformin or thiazolidinediones, two substances which exert their effects in hepatocytes and first of all lifestyle changes are the most promising therapeutic options.

O-16
Metabolic syndrome: a disease of the brain

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Introduction: Association between brain dysfunction and pathogenesis of metabolic syndrome leading to cardiovascular diseases, type 2 diabetes and insulin resistance are reviewed. Methods: Medline search for articles published in various national and international journals were reviewed. Experts working in the field were also consulted. Results: Excess of refined starches, linoleic acid, trans fat, saturated and total fat and low dietary n-3 fatty acids and other long chain polyunsarurated fatty acids (PUFA) in conjunction with sedentary behavior and mental stress and various personality traits can enhance sympathetic activity and increase the secretion of catecholamine, cortisol and serotonin that appear to be underlying mechanisms of metabolic syndrome. Excess secretion of these neurotransmitters in conjunction of underlying long chain PUFA deficiency, may damage the liver, heart, vessels, neurons via proinflammatory cytokines, in the ventromedial and lateral hypothalamus and insulin receptors in the brain, especially during fetal life, infancy and childhood, resulting into their dysfunction. Since, 30-50% of the fatty acids in the

brain are long chain polyunsaturated, especially omega-3 fatty acids, which are incorporated in the cell membrane phospholipids, it is possible that their supplementation may be protective.Omega-3 fatty acids are also known to enhance parasympathetic activity and increase the secretion of anti-inflammatory cytokines IL-4 and IL-10,as well as acetylecholine in the hippocampus. It is possible that marginal deficiency of long chain polyunsaturated fatty acids, especially n-3 fatty acids, due to poor dietary intake during the critical period of brain growth and development in the fetus and infant, and also possibly in the child, adolescents and adults, may enhance the release of tumor necrosis factor-alpha,interleukin-1,2 and 6 and cause neuronal dysfunction. Experimental studies indicate that ventromedial hypothalamic lesion in rats induces hyperphagia, resulting into glucose intolerance and insulin resistance. Treatment with neuropeptide Y abolished the hyperphagia and ob mRNA (leptin mRNA) in these rats. Longterm infusion of norepinephrine and serotonin into the ventromedial hypothalamus, impaired pancreatic islet function in as much as, ventromedial hypothalamic norepinephrine and serotonin levels are elevated in hyperinsulinemic and insulin resistant animals. Treatment with insulin was associated with restoration of these hypothalamic neurotransmitter abnormalities indicating that a dysfunction of ventromedial hypothalamus can impair pancreatic beta cells resulting into metabolic abnormalities consistent with metabolic syndrome.Treatment with omega-3 fatty acids, meditation, beta blockers, ACE inhibitors, may have a beneficial influence on insulin receptors and ventromedial hypothalamic dysfunction. However, no definite and precise insight into the patho-physiological link between metabolic syndrome and brain and nutrition is available. Despite this weakness, epidemiological studies and intervention trials indicate that treatment with n-3 fatty acids may be applied to clinical practice and used to direct therapy for prevention of type 2 diabetes, hypertension, coronary artery disease, and atherosclerosis, indicating that metabolic syndrome may also respond to this treatment.

O-17

A grape polyphenol extract reduces liver lipid content in rats fed a high fat-high sucrose diet: the SIRT1/AMPK signaling pathway

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Nonalcoholic fatty liver is one of the most common liver diseases in the world. Recent studies demonstrated that resveratrol may prevent against liver lipid accumulation through activating SIRT1 deacetylase, which regulates AMPK signaling pathway. The present study was designed to evaluate the effect of a grape polyphenol (PP) extract on liver lipid content and on the SIRT1/AMPK signalling pathway in rats fed a high fat-high sucrose diet. In that aim, 24 male Wistar rats were randomized into three groups of 8 animals; a control group (control) was fed for 6 wk a semipurified diet, a high fat high sucrose group (HFHS) was fed for 6 wk a high fat high sucrose diet and a PP group (HFHS+PP) was fed for 6 wk a high fat high sucrose plus 0.2% ProvinolsTM. ProvinolTM is a powder PP extract obtained from red wine that contains 0.15% resveratrol. Liver triglycerides (TG) content was measured by spectrophometric technique. Protein expression of SIRT1 (Silent Information Regulator), AMPK (AMP-activated protein kinase) and p-AMPK, p-ACC (AcetylCoA Carboxylase) and FAS (Fatty Acid Synthase) were measured by western blotting. mRNA expression of MCD (malonyl-CoA decarboxylase), CPT1 (Carnitine PalmitoylTransferase), MCAD (Medium Chain acyl CoA Dehydrogenase) and of PGC1 (peroxisome-proliferator-activated receptor-gamma co-activator) were measured by qPCR. Our results demonstrated that the PP extract partially prevent the accumulation of TG in liver. SIRT1 expression was significantly increased with PP by comparison to the HFHS and the control group. Moreover, expression of AMPK was higher with the PP supplementation by comparison to the HFHS, but no modification of p-AMPK was observed, maybe because of the high variabilty intra-group. The p-ACC, a key enzyme in lipid metabolism, was decreased in HFHS rats and return to basal values with the PP supplementation. mRNA expression of MCD, CPT1 and MCAD, involved in

the beta oxidation of fatty acids in the mitochondria, were not modified by the HFHS diet or by the PP supplementation. Finally mRNA expression of PGC1, a nuclear receptor coactivator that may mediate lipid homeostasis, was unchanged. This study demonstrated that the PP extract regulates ACC phosphorylation, a key enzyme in the lipid metabolism, probably via the SIRT1/AMPK signalling pathway activation.

O-18
Prevalence and risk factors of focal sparing in hepatic steatosis

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Prevalence, localization and potential risk factors for focal sparing were prospectively assessed in subjects with sonographically detectable hepatic steatosis as part of a population-based cross-sectional study. Material and Methods: A total of 1,624 persons were evaluated using ultrasonography, laboratory testing and a standardized questionnaire. Excluded from the analysis were subjects with reported alcohol consumption >40 g/day (males) or >20 g/day (females), those with known chronic hepatitis B or C infection, elevated serum transaminases (AST: m>44U/l, f>33U/l; ALT: m>45U/l, f>35U/l) and prior right nephrectomy. Results: Prevalence of focal sparing in patients with hepatic steatosis (grade I) was 26.5% for men and 13.0% for women; in patients with grade II/III disease, the prevalence was 70.9% for men and 77.6% for women. The most common site of focal sparing was in segment IV. The average diameter was 22.3 mm (range 7-84 mm). No correlation was found for postulated risk factors "Age" (p=0.09) or "Status post Cholecystectomy" (p=0.09). Male sex (p=0.02) and metabolic syndrome (modified ATP III criteria) (Odds ratio, 2.1; 95% confidence interval, 1.1-4.1; p=0.02) were confirmed as risk factors. Conclusions: Sonographic evidence of focal sparing in subjects with hepatic steatosis is associated with an increased risk for metabolic syndrome and maybe an easily obtained diagnostic criterion in routine clinical settings.

O-19

Exercise increases liver fatty acid oxidation and prevents steatosis in tumour-bearing rats

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The effect of endurance training on hepatic carnitine palmitoyltransferase (CPT) system activity was studied in tumor-bearing (Walker 256 carcinosarcoma) rats. Animals were randomly assigned to a sedentary control (SC), sedentary tumor-bearing (ST), or exercise control (EC) and exercise tumor-bearing (ET) group. Trained rats ran on a treadmill (60%VO2max) for 60min/day, 5 days/week, for 8 weeks. We examined the mRNA expression and maximal activity of the carnitine palmitoyltransferase system enzymes (CPT I and CPT II) and the mRNA expression of fatty-acid binding protein (L-FABP) and cyclooxygenase type 2 (COX-2) in the liver. PGE2 content was measured in the serum, liver and tumor. Results: CPT I and CPT II maximal activity was decreased ($p<0.01$) in ST (2.66±0.0 and 0.16±0.10 nmol min-1mg-1protein, respectively) when compared with SC (3.66±0.38 and 1.68±0.16 nmol min-1mg-1protein, respectively). In contrast, liver COX-2 mRNA of cachectic animals was increased, as well as PGE2 in serum (2.526±0.132 ng/mL, $p<0.05$), as compared to SC (1.901±0.259 ng/mL). In the liver PGE2 levels found were increased (2.030±0.047 ng.ug protein^{-1}, $p<0.05$) when compared to SC (0.997±0.036 ng.ug protein^{-1}). Exercise restored maximal CPT I and CPT II activity in tumor-bearing rats (10.61±1.62 and 9.25±1.12 nmol min-1mg-1protein, respectively, $p<0.0001$), when compared to ST. Also, the protocol restored PGE2 levels in the liver of tumor-bearing training rats (1.150±0.053 ng.ug protein-1, $p<0.05$) and decreased tumor levels (ET: 2.750±0.096 ng.ug protein-1 vs ST 4.580±0.088 ng.ug protein-1, $p<0.01$). COX-2 mRNA expression was decreased in the liver of exercised tumor-bearing rats when compared with the sedentary counterparts.

In conclusion, endurance training was capable to promote the reestablishment of liver mitochondrial carnitine palmitoyltransferase (CPT) system activity due to a decrease in PGE2 levels in cachectic tumor-bearing animals, preventing steatosis.

O-20
Molecular mechanism of petrochemical-induced non-alcoholic fatty liver

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Our long-term studies of a chemical/virus mouse model of acute liver failure reveal that chronic exposure to petrochemicals, major constituents of most pesticide formulations, leads to hepatic steatosis. Mice exposed dermally to the pesticide adjuvant, Toximul (Tox), for 12 days exhibit no obvious adverse health effects; however, signs of liver dysfunction include transient hyperammonemia and hepatomegaly. Most dramatically, hepatic energy metabolism is greatly compromised by Tox exposure, with significantly ($p<0.05$) reduced levels of glycogen (~50%) and fatty-acid oxidation activity (~25%). Body weights are either unchanged or reduced by Tox treatment; however, all mice have significantly higher liver: body weight ratios (~12%) due to accumulation of lipid that is endogenous in nature and/or a components or metabolite of Tox. This study is the first to investigate the mechanism underlying petrochemical-induced fatty liver. We demonstrated that dermal exposure to Tox alters the expression of enzymes regulated by the 'master switch' controlling lipid metabolism, peroxisome proliferator-activated receptor alpha (PPARα). Prolonged petrochemical exposure increased expression of mRNA coding for peroxisomal acyl-coenzyme A oxidase, bifunctional protein and thiolase, as well as for microsomal Cyp4A, the enzymes involved in dicarboxylic acid clearance. Involvement of PPARα in these changes was confirmed, as the effects occurred in wild type but not in corresponding PPARα null mice. We propose that the liver responds to exposure to xenobiotic hydrocarbons by increasing expression of lipid catabolizing enzymes, but that the products yielded cannot be cleared

from the liver; the consequence is hepatic fat accumulation. The results of our studies provide new insight into the etiology of fatty liver in populations exposed to persistent environmental pollutants, including those in the agricultural and petrochemical industries. (Supported by NSERC)

O-21
Fatty degeneration and acute liver failure with valproic acid and duloxetine

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Valproic acid (VPA) has been used as an anticonvulsant for more than 30 years. Meanwhile, VPA has also been approved by the FDA for treatment of bipolar disorder and migraine. We report the case of a 58-year-old female patient who died from liver failure probably due to treatment with VPA. The patient was admitted for bipolar affective disorder, currently depressed. Clinical examination, ECG, cranial MRI and laboratory results were normal. Long-term treatment with candesartan for arterial hypertension was well tolerated. Duloxetine was introduced as an antidepressant, VPA as a prophylactic treatment. On day 7 of VPA treatment, VPA serum level was 73 mg/l and liver function tests were normal. 18 days after starting treatment with VPA, the patient was admitted to a medical emergency unit due to diarrhea, gait ataxia and elevated temperature. Liver enzymes (AST 8747 U/l, ALT 7184 U/l, GGT 153 U/l) and creatinine (332 µmol/l) were elevated. VPA serum level was 81 mg/l. Hepatitis serology and auto-antibodies were negative. Sonographically, pancolitis with acute nephropathy, mild splenomegaly and minor pleural effusion were evident. A CT scan revealed edematously enlarged kidneys, increased mesenterial lymph nodes, and a normal liver. Due to acute liver failure, liver transplantation became necessary and was performed 12 days after admission to the medical emergency unit. Histologically, extensive necrosis was

demonstrated, with less than 5% of liver tissue preserved. Plasma cell infiltration and fatty degeneration of hepatocytes were found. A second transplantation became necessary, and the patient died of sepsis and multi-organ failure after five months. In this patient, liver failure occurred within less than three weeks after the introduction of VPA and duloxetine. No other risk factors could be identified. The present case suggests that monitoring of liver enzymes four weeks after initiating VPA therapy might be insufficient.

O-22
Oxidative stress and mitochondrial dysfunction are associated with the opening of permeability transition pore in a rodent model of NAFLD

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Mitochondria play an important role in the pathogenesis of non-alcoholic fatty liver disease (NAFLD). Hepatocytes apoptosis has been described in NAFLD patients. The mitochondrial permeability transition pore (PTP) is an inner membrane channel which regulates cellular pathways involved in apoptosis. PTP opening is associated with the release of cytochrome c (cyt c) and caspases activation. We aimed to study the PTP opening in a rodent model of NAFLD and the factors that modulate its permeability. Methods: NAFLD was induced by feeding Wistar rats a methionine and choline deficient diet (MCD). Liver mitochondrial membrane potential (MMP) was measured using a TPP+ electrode, and mitochondrial lipid composition by gas-chromatography. We also measured in mitochondria H2O2 production and hydroxynonenal (HNE)-protein adducts by fluorimetric analysis. Hepatic ATP content was also determined. PTP opening was measured spectrophotometrically. Results: in NAFLD liver, MMP was reduced; docosapentaenoic and docosahexaenoic acids were increased, and oleic, linoleic and arachidonic acid were decreased. Moreover, we reported increased H2O2 production and mitochondria HNE-protein adducts. Hepatic ATP content was reduced in NAFLD. In liver

mitochondria from NAFLD rats PTP opening occurred at lower concentrations of Ca++ as compared to controls, as well as cyt c release. Discussion: during NAFLD, opening of the mitochondrial PTP and cyt c release are associated with impairment of mitochondrial bioenergetics, as demonstrated by reduced MMP and hepatic ATP content. Moreover, these alterations are associated with mitochondria hydrogen peroxide production and membranes modifications, which induce lipid peroxidation, HNE production and progression of oxidative damage. Taken together, these changes may lead to the activation of apoptotic mitochondrial pathways.

O-23
L-carnitine counteracts cancer cachexia-associated steatosis in rats

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Cachexia is a chronic inflammatory syndrome, characterized by marked weight loss and abnormalities in intermediary metabolism. Disruption of liver lipid metabolism, comprising higher uptake of long-chain fatty acids (LCFA), along with diminished oxidation and incorporation into very low density lipoproteins (VLDL), results in steatosis, aggravating cachexia. L-carnitine is required for the transport of LCFA into the mitochondria, and cachectic animals and patients present decreased plasma carnitine concentration. L-carnitine supplementation is adopted in the treatment of many diseases, and we sought to examine whether cachectic rats would benefit from this strategy. 24 male Wistar rats were inoculated with the Walker 256 carcinosarcoma (2 x 10^7cells) and divided into 2 groups: supplemented with L-carnitine (1g/Kg gavage, for 28 days)-TBC, and control (receiving saline),-TB. 24 non-tumour-bearing rats were divided into a L-carnitine supplemented group –NC, and the respective control –N. Liver and plasma triacylglycerol (TAG), liver mRNA expression (semi-quantitative RT-PCR) of carnitine palmitoyltransferase I and II (CPT I and II), microsomal triglyceride transfer protein (MTP), fatty acid-binding protein (L-FABP), fatty acid translocase (FAT/CD36) and peroxisome proliferator-activated receptor-alpha (PPARα), and the maximal activity (radioassay) of CPT I and II (the key step in LCFA oxidation), were evaluated. Gene expression of MTP and CPT I activity were reduced in TB (6%,

$p<0.05$, and 42%, $p<0.01$, respectively). TB also showed increased ($p<0.01$) liver and plasma TAG content in relation to N. Chronic treatment with L-carnitine restored mitochondrial LCFA oxidation ($p<0.01$) and VLDL assembly capacity, suppressing cachexia-related hypertriglyceridemia ($p<0.001$) and steatosis. Attenuation of cachexia was accompanied by reduced tumour weight (62%) after supplementation. The results indicate that L-carnitine improves liver lipid metabolism in cachexia.

O-24

Fluorescence spectroscopy to diagnoses hepatic steatosis in a rat model of fatty liver

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O-25

The need for an international NAFLD-Index

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O-26

APRI is not useful in predicting hepatic fibrosis in non-alcoholic fatty licer disease: experience from a tertiary centre in Bangladesh

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Background and aims: The search for a novel, non-invasive alternative to liver biopsy continues. APRI correlates with fibrosis in CHC. This study was to see whether the same applies in NAFLD. Methods: 62 patients with NAFLD were included. In all platelet count (PC), ALT (cut off 42 U/

L) and liver biopsy were done. APRI was calculated in every patient by ALT x UNL x 100/PC x 10^9/L. APRI was compared between those with fibrosis ≥2 and fibrosis <2. Results: 53.3% were males and 46.7% females. They were between 20-60 years of age. 93.3% had fibrosis <2 and 6.7% had ≥2. In fibrosis <2, 35.7% had ALT <40 IU/ml, 32.1% had 40-50 IU/ml and 32.1% had >50 IU/ml. In fibrosis ≥2, 50% had ALT >50 IU/ml. High fibrosis was not associated with high ALT in majority. In fibrosis <2, 14.3% had ALT <40 IU/ml and 64.3% >50 IU/ml. On the hand, in fibrosis ≥2, these figures were 50%. Based on PC, patients were divided into 2 groups, <150,000/cumm and ≥150000/cumm. In fibrosis <2, 10.7% had PC <150000/cumm and 89.3% had ≥150,000/cumm. 100% patients with fibrosis ≥2 had PC ≥150000/cumm. When we consider APRI >0.5 indicates fibrosis ≥2, 48.4% cases were diagnosed, but not confirmed at histopathology. They were false positive. Of the remaining cases with fibrosis <2 diagnosed by APRI, 3.2% were confirmed at histopathology. Sensitivity of APRI (cut off level >0.5) to diagnose fibrosis ≥2 was 50.0%, specificity 46.4%, positive predictive value 6.3%, negative predictive value 92.9% and accuracy 46.7%. When we consider APRI >1.5 indicates fibrosis >2 (cut off value >1.5), 3.2% were diagnosed as fibrosis ≥2, but not confirmed by histopathology. These were false positive. Of 93.5% cases with fibrosis <2 diagnosed by APRI, 6.4% were confirmed as fibrosis ≥2. Sensitivity of APRI (cut off level >1.5) to diagnose significant fibrosis was 0%, specificity 96.4%, positive predictive value 0%, negative predictive value 93.1% and accuracy 90.0%. Conclusion: Though APRI has good predictive value for predicting significant fibrosis in CHC, it seems unlikely that APRI will be the answer in NAFLD.

O-27

Acetaminophen disposition: a novel metabolomic biomarker for non-alcoholic fatty liver disease

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Non-alcoholic fatty liver disease (NAFLD) includes a range of pathologies from simple steatosis to steatohepatitis (NASH). Researchers estimate the prevalence of NAFLD to be 20-25% and NASH at 2% of the US population. NAFLD has been linked to obesity, and with childhood obesity rates increasing drastically, the number of children with severe liver disorders continue to grow. One obstacle to proper treatment is the inability of clinicians to easily distinguish between simple steatosis and NASH. Currently, needle biopsy is the only conclusive method of diagnosing and staging NAFLD. A key concern with NASH is the possibility that altered hepatic function could interfere with proper elimination of therapeutic drugs leading to toxicity. Previous work from our laboratory using a rodent model of NASH indicated changes in the disposition of acetaminophen (APAP) metabolites, where an increase in the expression of the sinusoidal efflux transporter Mrp3 leads to elevated plasma and urinary levels of APAP-glucuronide. The current study was conducted to determine whether human NAFLD also results in altered disposition of APAP and APAP metabolites. Adolescent patients with mild and severe NAFLD and normal patients were given a single 1000 mg dose of APAP. Blood and urine samples were collected over time and the levels of APAP and APAP metabolites were determined by HPLC. As with the rodent model of NASH, patients with the more severe disease (steatosis, inflammation, fibrosis) had significantly increased plasma and urinary levels of APAP-glucuronide. Additionally, adult post-mortem NASH liver samples exhibited increased levels of Mrp3 protein. These findings corroborate the validity of the NASH animal model, and present the possibility of a non-invasive diagnostic tool for the advanced stages of NAFLD. (Supported by DK068039 and ES007091)

O-28

Higher serum dipeptidyl peptidase-4 activity and insulin resistance index in non-alcoholic fatty liver disease than in type-2 diabetes without liver disease in patients with similar degree of obesity

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DPP-4 inhibitors were introduced in the treatment of type 2 diabetes mellitus (T2D) and increased serum DPP-4 activity (sDPP-4) was reported in chronic liver diseases. We studied the sDPP-4 and the insulin resistance index (HOMA2-IR) in patients (pts) with T2D and non-alcoholic fatty liver disease (NAFLD) and in healthy controls (CNTRL). Materials and Methods: sDPP-4 activity was measured by kinetic assay in 39 NAFLD (F/M:19/20, mean age: 47.42 yrs) and 86 T2D (F/M:50/36, 62.8yrs) pts and 23 (F/M:12/11, 35.33yrs) CNTRL. We excluded those pts from the T2D group who were clinically with liver disease. All NAFLD pts -except the 9 previously diagnosed with 2TDM- underwent 75g CH OGTT. Insulin resistance index (HOMA2-IR) was calculated by the computational method. Parametric statistical tests were used. Results: Pts in the T2D and the NAFLD groups were with similar degree of obesity. OGTT in 39 NAFLD pts: 24 NGT, 4 IGT or IFG and 11 type 2 diabetes. HOMA2: CNTRL: 1.44 - T2D-: 2.60 ($p=0.023$ vs. CNTRL) - NAFLD with NGT only: 3.23 ($p=0.0013$ vs CNTRL) and NAFLD with IFG/IGT/2TDM: 3.82 ($p<0.0001$ vs CNTRL, $p=0.044$ vs. 2TDM group). sDPP-4 activity was higher in NAFLD pts both with NGT (mean:33.08U/L) and abnormal glucose metabolism (30.38U/L) than in CNTRL (25.89U/L, $p<0.001$ and $p=0.013$) or in T2D (without liver disease) (24.11U/L, $p<0.001$ and $p=0.002$). Correlations were detected among sDPP-4 and ALT ($r=0.4637$, $p=0.0038$) and gGT ($r=0.4991$, $p=0.0017$) and HOMA2-IR ($r= 0.5295$, $p=0.0026$) and among the HOMA2-IR and ALT ($r=0.4340$, $p=0.0147$) and gGT ($r=0.4128$, $p=0.0210$) in NAFLD. Conclusions: Serum DPP-4 enzyme activity was increased in NAFLD and correlated with liver tests in NAFLD supporting that the excess is of hepatic origin. Based on the association of liver tests and HOMA2-IR and on the higher HOMA2-IR values in NAFLD than in the similarly obese T2D pts without liver disease we concluded that liver disease should contribute to the development of insulin resistance.

O-29
Does the carbohydrate deficient transferrin have a diagnostic value in non alcoholic fatty liver?

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The non alcoholic fatty liver (NAFLD) is an acquired metabolic liver disease in the consequence of triglyceride accumulation within the liver cells. It is accompanied by necrobiotic inflammatory reaction, fibrosis and also by liver cirrhosis. Its differentiation from alcoholic fatty liver (AFLD) seems sometimes to be difficult. It is simple knowing the clear anamnesis, but if the individual do not want to inform us about the alcohol consumption, the differentiation is not very easy. Aim of the study: The aim was to determine the value of carbohydrate deficient transferrin (CDT) in patients with non alcoholic fatty liver, as well as to analyze the high values according to the anamnesis. Patients and methods*:* The group of patients consisted of 39 individuals, whose ultrasound examination showed the signs characteristic to fatty liver. The sex rate was: 21 female and 18 male patients. The values of CDT, body mass index (BMI) and HOMA index were determined. The mean value of CDT was: 239 ± 0.52 % (in male 2.51 ± 0.61, in female 2.28 ± 0.4). No significant difference was found among the two sexes. The diversity of CDT values was normal. The value of BMI belonged to the overweight area without any significant difference between the two sexes. Conclusion: On the basis of the results the NAFLD and the AFLD can be differentiated according to the CDT value, and this value could be a higher specific value than the activity of gammaglutamyl transpeptidase, though also in this relation the valuations of anamnesis and other factors are very important for achieving the correct diagnosis.

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O-30
Utility of FSI in documenting fibrosis in NASH

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NAFLD is the most common liver disorder in Western industrialized countries and NASH refers to those NAFLD patients with some degree of fibrosis. Currently, the best way to identify patients with fibrosis or scarring is a liver biopsy. A special blood test which we have developed, the "Fibrogenic Stimulation Test (FSI)" can identify patients with fibrosis or liver scar. With collaborators from other countries, we will investigate the utility of FSI in documenting the fibrosis associated with NASH. We will investigate the FSI in a target group where the prevalence of diabetes was far higher than in the general population, since diabetes affects nearly 200 million people worldwide and is highly associated with and a risk factor for NAFLD. NASH is the liver component of the metabolic syndrome associated with diabetes. Detection of fibrosis in these patients may allow for early intervention. We want to assess the FSI and Fibroscan in these patients. At present there are very few therapeutic options for patients NASH. We have developed a screening test system "Drug Inhibition Index (DII)" where we can test many drugs in vitro to see if these drugs can reduce the liver scar producing potential. With cooperation from other centers we will investigate new therapeutic options for NASH using the DII. We have shown that DII predicted the beneficial effect of pentoxifylline in controlling scarring. In order to further our understanding of the disease process, we will investigate using state of the art molecular techniques the mechanism of action of potential antifibrotic drugs which have direct significance in diabetes. Pentoxifylline also improves and prevents fibrosis formation in an animal model of liver fibrosis. As this is a largely under-studied area of research, the data will have direct significance in NASH and could potentially decrease the high morbidity and mortality associated with NASH in diabetes. Our extensive research indicates that FSI is an excellent tool to predict fibrosis. Our data suggests that FSI correlates with P-III-P and fibrosis score and is a positive predictor of fibrosis in HCV patients. We will contrast the FSI to Fibroscan, a diagnostic test for detecting hepatic fibrosis, in this target population. Objectives:

The major aim is to assess the FSI and transient elastography in a group where the incidence of diabetes far exceeds the norm. These parameters will be correlated with P-III-P and histological analysis of liver biopsies and contrasted to Fibroscan results. We will also assess the DII of potential anti-fibrotic agents including pentoxifylline. We will characterize the molecular events involved in the stimulation of fibrosis in hepatic stellate cells (HSCs). A knowledge translation aspect of this project will link at-risk individuals with a dietician for counseling for the management of liver disease secondary to diabetes and the www.StreetGuru.ca website. Hypotheses: FSI is a reliable, definitive, accurate index of fibrosis in this patient population. The incidence of NASH may be higher in this group, reflecting the higher incidence of diabetes. Drugs, such as pentoxifylline, will reproducibly decrease the FSI and be effective antifibrotic drugs. Molecular characterization of the FSI in HSCs will define the mechanism of action of drugs and provide novel targets for new antifibrotic drugs in NASH. Study Proposal and Design: The studies will be largely non-invasive, requiring a blood sample to do the FSI. We plan to do in vitro studies and invite the inclusion of other investigators and other centres: to establish the effect of pentoxifylline and related drugs, and drugs currently used to treat diabetes (both alone and in drug combination) on DII for patients with NASH. 2) to determine the incidence of NASH associated fibrosis in the community that have a high incidence of diabetes using the FSI, P-III-P and the Fibroscan. 3) to characterize the molecular events in HSCs. Significance and Future Direction: The proposed studies are designed a) to ultimately assess the extent of fibrosis without a liver biopsy in the patients with NASH by use of FSI and/or Fibroscan, b) to predict the response to treatment with novel antifibrotics, c) to understand the incidence of fibrotic disease in these patients who have a higher incidence of diabetes, d) to understand disease mechanism using a molecular approach and translate the molecular information obtained into potential new targets for new antifibrotic drugs. Knowledge translation is an important aspect of this study as we anticipate that the complex molecular information obtained will be translated into screening tests and potential new therapy and critical information for patients with the potential to develop fibrotic disease associated with NASH.

O-31
Using Two Criteria to Assess the Prevalence of Metabolic Syndrome (MS) among Male Kuwaiti Adolescents

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O-32
Ultrasound in the diagnostics of fatty liver in obesity

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Ultrasound (US) has basic significance in the diagnostics of chronic diffuse liver diseases (CDLD) by the characteristic image of bright liver in these cases. On the basis of liver US attenuation (α) two major groups of bright liver can be separated, the low (DI) and the high (DII) α type. During US examination of the patient α is measurable by the use of a reference phantom (RPh) and appropriate software. It was proved previously that DI type shows increase of connective tissue content, while DII type is associated with fatty liver, which is one of the major complications of obesity. The question arises, whether a cut-off value can be defined between the two α types and that of the normal livers as well. 432 patients with CDLD (proved by clinical, laboratory and histological data) were examined by US and α was also measured. Further, subcutaneous fat thickness (SCF), visceral fat thickness (VFT), intima-media thickness (IMT) of the common carotid artery, and thyroid parameters were also studied. Abnormal values of some of these parameters may indicate cardiovascular complications. 125 normal livers, 176 DI and 130 DII type bright livers were found. In cases of normal livers α values never reached 1 dB/cm/MHz. In DI type bright liver cases α were always under 1.1 dB/cm/MHz showing strong overlap with normal liver values. α of DII type were higher than 1.1 dB/cm/MHz, thus fatty liver can be differentiated from normal as well as DI type bright livers. α values were strongly corre-

lated with BMI and SCF, which are also signs of fatty liver. The presence of fatty liver is not certainly connected with cardiovascular complications. It can be concluded, that above 1,1 db/cm/MHz α value, defined as cut-off, the diagnosis of fatty liver can be established with high reliability without obligate histological investigation. Clinical research projects based on α measurements give new information about fatty liver in obesity.

O-33
Therapy modalities in non-alcoholic steatohepatitis

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Hepatic steatosis involves an imbalance between the processes of the hepatocytes' lipid uptake and lipid elimination, an overproduction results in the accumulation of excess triglycerides in the cells of the liver. Normally about 5% of the cells contain triglyceride; in steatosis this may exceed 50%. Under 50% the condition is called fatty infiltration, and over 50% it is called fatty liver. In mild forms this does not necessarily lead to disorders in cell functions, but in more severe forms it does; it often precedes the death of the cell. Fatty liver can be considered a pathologic condition which makes the liver more susceptible to other toxic influences. It is not a genuine disease; in most cases it is associated with a noxious state or other pathologic process. The abnormal accumulation of fat in parenchymal organs, including the liver, is called fatty transformation or steatosis. Alone and limited to a certain degree of severity (the appearance of fibrosis), it represents a reversible damage; upon cessation of the underlying cause the liver clears its excess triglyceride content. The treatment is to be aimed at the underlying process; up to now there is no known specific medicine that could clearly reduce the fat accumulated in the hepatocytes. Although the etiologic factors of these diseases differ from each other, the pathological changes in the liver are very similar, thus certain drugs could be equally effective for treating tehm. The importance of the changes in lifestyle cannot be emphasised enough both in NASH and in the metabolic syndrome. A gradual reduction of body weight (by 0.45 to

0.9 kg/week) combined with exercise therapy improves insulin resistance, leading to the mitigation the histological alterations of NASH, and diminishes the risks of complications of the metabolic syndrome as well. In addition to a weight loss program designed by a professional, also medicines helping weight loss (sibutramine, orlistat) may be administered. Improving control of carbohydrate metabolism is of crucial importance in the metabolic syndrome, and it seems to be the same in NASH, as well. Correction of lipid disorders should also be taken into consideration. The principal role in the therapy of NASH is currently represented by the treatment of diabetes, hyperlipidaemia, and obesity, together with antioxidants, like ursodeoxycholic acid (UDCA), silymarin as well as metadoxine. Metadoxine is one of those drugs, mainly due to its liver-protective effect against damage from free radicals. As an effective antioxidant, metadoxine regulates glutathione levels in the liver and throughout the body, thus positively influencing the maintenance of systemic redox homeostasis. The results with UDCA significantly reduced the levels of enzymes showing hepatocellular damage. Similar results are known with silymarin-type natural radical scavengers.

The work is closely associated to the EU Project *"COST B35 Action: Lipid Peroxidation Associated Disorders: LPO"*.

O-34

Metabolic syndrome - a ghost with real weapons?

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O-35

The relevance of lipid peroxidation in liver pathopysiology

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O-36
Lipid oxidation, inflammation and fibrosis

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O-37
Comparison of tumorogenicity of liver and kidney tumors induced by N-nitrosodimethylamine in rats

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O-38
Protein kinase C beta (PKCbeta) plays an important role in regulating whole-body's triglyceride homeostasis

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O-39
Lipid oxidation and fibrogenesis in cancer progression

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O-40
Obesity and fatty liver

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The global emergence of obesity as an epidemic has made fatty liver disease a public health problem. The increased incidence of obesity has been paralleled by an increase in metabolic syndrome in the same cohort of patients. The net consequence of insulin resistance (IR) in a large majority of these obese individuals is hepatic steatosis, which over time in a proportion of these patients progresses to steatohepatitis. The link between obesity and the development of fatty liver has also been well documented with numerous studies showing that 70 to 80% of people with body mass index >30 kg/m^2 have hepatic steatosis. Obesity and insulin resistance are the major risk factors for nonalcoholic hepatic steatosis, which presents in 30-90% of the population. Around 10-20% of these patients are carriers of nonalcoholic steatohepatitis (NASH), which might progress to cirrhosis in 3-5% of the patients after 20 years. High calorie consumption in sedentary and genetically susceptible individuals induces lipolysis, tumour necrosis factor-α (TNF-α) expression and hypoadiponectinemia, leading to peripheral insulin resistance and an increased circulating fatty acid pool. Hepatic fat deposition induces insulin resistance per se through abnormal intracellular insulin signalling. Both these processes lead to hepatic insulin resistance and fatty deposition with increased expression of sterol-regulatory element-binding protein-1c (SREBP-1c), endocannabioid receptor CB1 and probably ghrelin, all of them capable of inducing de novo hepatic lipogenesis. Increased fatty acid availability activates mitochondrial, peroxisomal and microsomal oxidation, leading to increased production of reactive oxygen species, which in turn induces lipid peroxidation, protein denaturation and DNA damage and induces apoB proteolysis, decreasing hepatocellular triglyceride export favouring steatosis. Future prospects of therapy are based on a better knowledge of NAFLD pathophysiology, particularly on the role of oxidative stress and certain adipokines such as TNF-α and adiponectin. Integrated health interventions are advisable aiming to promote lifestyle changes among the general population.

O-41
The effect of statins on the hepatocyte function

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O-42
Statins in the therapy of fatty liver

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Nonalcoholic fatty liver disease (NAFLD) is the most common liver disease worldwide. The fundamental derangement in NAFLD is insulin resistance, a key component of the metabolic syndrome, which include type 2 diabetes mellitus, dyslipidemia, hypertension, and obesity. NAFLD includes various liver diseases from steatosis and steatohepatitis to cirrhosis. According to results to date, NAFLD is considered an independent cardiovascular risk factor, therefore lowering cardiovascular risk without any side-effects is especially important in these patients. Lowering LDL cholesterol levels is of crucial importance in the primary and secondary prevention of cardiovascular diseases. In relation to 3-hydroxi-3methylglutaryl-coenzyme A-reductase (HMG-CoA reductase) i.e. statins, used for the treatment of dyslipidaemia, several large-scale, randomized studies have proved to significantly reduce cardiovascular risk and also events. An important issue regarding the use of statins in patients with NAFLD is their potential hepatotoxicity. However, increasing evidence suggests that the use of standard doses of statins in these patients with elevated liver enzymes is not associated with a significantly increased risk of serious hepatotoxicity. Thus, statins are likely to play an increasing role in the overall management of patients with NAFLD. Despite their potential significance, the cellular effects of statins in NAFLD have not been elucidated.

The work is closely associated to the EU Project *"COST B35 Action: Lipid Peroxidation Associated Disorders: LPO"*.

O-43
Estrogen receptor variants may be implicated in carcinogenesis and progression of human hepatocellular carcinoma

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O-44
Hepatitis C virus infection and lipid metabolism

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O-45
Hepatitis C virus-induced steatosis

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O-46
Fatty liver and respond to combined peginterferon and ribavirin treatment

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In the treatment of chronic liver diseases an adequate therapy could be chosen only in the knowledge of the pathogenetic processes. In liver diseases caused by oxidative stress (alcoholic and non-alcoholic fatty liver and steatohepatitis, drug- and chemical-induced hepatic toxicity) the anti-

oxidant drugs such as silymarin, ursodeoxycholic acid, metadoxine are the therapeutic modalities, in chronic hepatitis caused by hepatitis B and hepatitis C virus the combined pegylated interferon and nucleoside analogue treatments are the primary drugs of choice. The overweight/obesity is an independent negative predictive factor of steatosis in chronic hepatitis C virus infection. The nonresponse to combined peginterferon and ribavirin treatment in infection caused by genotype 1 is associated with the waist circumference, body mass index (BMI), diabetes, steatosis, and degree of fibrosis. Obesity may alter cytokine function and interferon signaling in the liver, and may decrease bioavailability of interferon. Hepatic steatosis decrease contact between the antiviral drug and infected hepatocytes. Leptin resistance may alter the T-cell response, decreasing the potential for viral clearance. Insulin resistance is an important factor leading to steatosis, fibrogenesis and increased HCV replication. According to open studies the long-term administration of silymarin significantly increased survival time of patients with alcohol-induced liver cirrhosis. Recently it has been demonstrated that high-dose silibinin infusion treatment could significantly reduce viral load of hepatitis C viruses following four weeks of application. Based on the results of studies silymarin can significantly reduce tumour cell proliferation, angiogenesis as well as insulin resistance. The author summarizes the importance of steatosis and insulin resistance in chronic HCV hepatitis as well as reviews the impact of weight reduction and the improvement of insulin sensitivity. *Conclusion:* Body-weight reduction and hepatoprotective drugs as well as the increase of insulin sensitivity with different medicines might have increased the effectivity of combined peginterferon and ribavirin treatment and thus the sustained virological respond.

The work is closely associated to the EU Project *"COST B35 Action: Lipid Peroxidation Associated Disorders: LPO"*.

O-46.a
Oxidative stress and antioxidant therapy in chronic viral hepatitis

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Since oxidative stress may play a pathogenetic role in chronic viral hepatitis, we recall our earlier data on the antioxidant flavonoid catechin in chronic hepatitis B, then we report a double blind study with silymarin, performed in pegylated interferon (PEG-IFN) + ribavirin (RBV) treated patients with chronic hepatitis C virus (HCV1) infection. Patients and methods: Thirty-two patients with chronic hepatitis C have been randomized: Group A): 16 patients were treated with PEG-IFN + RBV antiviral therapy for 6-12 months plus placebo for the first 3 months, Group B): 16 patients were treated with PEG-IFN + RBV for 6-12 months, plus silymarin 2 x 166 mg/day was given for 3 months. Serum alanine aminotransferase (ALT) and HCV-RNA levels, and parameters of oxidative stress such as plasma or red blood cell hemolysate malondiadehyde (MDA), superoxide dismutase (SOD), glutathione peroxidase (GPX), catalase and myeloperoxidase (MPX) were determined at 0, 1, 3, 6 and 12 months during the treatment. The sustained virological response (SVR) as undetectable serum HCV RNA was evaluated after 24 weeks of the end of therapy. Results: In the group B a more rapid decrease in MDA level, as well as a marked decrease in SOD, and an increase in MPX activity at month 12 were found. Although silymarin supportation to antiviral therapy improved oxidative stress parameters, it was not able to affect favourably neither ALT nor SVR. These contradictory findings may be related to randomization bias, as patients in the Group B have more negative predictors of response: they were older with higher fibrosis score and even with more severe pretreatment baseline oxidative stress. Yet, regarding the *in vitro* experiments of *Polyak et al*[1] with silybinin on HCV replication, and the newest convincing clinical observations published by *Ferenci et al*[2], we do suggest further studies with more than threefold doses of silymarin

in controlled trials to asses the value of this antioxidant supplementation in HCV patients receiving antiviral therapy.

[1]) Polyak SJ, Morishima C, Shuart MC et al,. Gastroenterology 2007; 132: 1925-1936.

[2]) Ferenci P , Scherzer TM, Hofer A et al., J. Hepatology 2008; 48: (suppl. 1) S28.

O-47

The negative role of insulin resistance for sustained virological response in chronic hepatitis C patients

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The response to pegylated interferon (PEG-IFN) and ribavirin (RBV) treatment in chronic hepatitis C virus (HCV) infection is influenced by various factors. Insulin resistance (IR), hepatic steatosis and overweight are associated with poor results. Aim: to analyze the association between the parameters of IR and the response to the antiviral treatment in HCV patients. Patients and methods: 87 HCV patients (37 male, M; 50 female, F; each genotype 1), mean age 46.8 (18-65) years were involved into the study. 19 patients had type 2 diabetes mellitus. Body weight, BMI (body mass index), waist circumference, HOMA (homeostasis assessment model) index, serum glucose and insulin levels were measured before the treatment. Liver biopsy was performed in 80 patients. Liver steatosis proved histologically was also considered. We compared these parameters both groups of responder and nonresponder patients. Results: The mean body weight was 74.5 kg; BMI 26.4; waist circumference 94 cm (M); 88 cm (F). The mean HOMA index was 4.6 (high). Overall sustained viral response (SVR) rate was 36% (M:27%, F:42%). High waist circumference was associated with low (33%) SVR, especially in males (21%). In patients with high HOMA values (>2.5) the rate of SVR was low (18/58, 31%) and hepatic steatosis was more common (47/55, 85%). SVR rate among the diabetic patients was only 16% (3/19). Poor SVR was detected in patients with abnormal ALT levels at week 12 (7/44, 16%). Conclu-

sion: IR and diabetes mellitus, high HOMA index, hepatic steatosis, high waist circumference and abnormal ALT at week 12 are the best negative host predictors of the sustained virological response beyond the virological factors (genotype, viral load). Prospective, large patient number studies are needed to evaluate the accurate role of the IR in sustained virological response in HCV patients.

O-48

Autonomic and sensory nerve functions during 48 weeks of anti-HCV treatment. A follow-up study

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Neurological complications of chronic hepatitis C virus (HCV) infection mainly change for the better during anti-HCV treatment, but they can worsen, as well. In our present study we investigated the changes of autonomic and peripheral sensory function in HCV patients during antiviral treatment. Methods. 21 HCV PCR positive, treatment-naive patients with no liver cirrhosis and no symptoms of peripheral or autonomic neuropathy were enrolled in the study (age=44.9±10.1 years). Cardiovagal autonomic function was assessed by determining heart rate variability (HRV) and baroreflex sensitivity (BRS) indices. Peripheral sensory nerve functions on median and peroneal nerves were characterized by current perception thresholds. Serum cryoglobulins and HCV-RNA level assessments were made. Interferon alfa-2 and ribavirin were given according to the guidelines. Measurements were made 1 day before first dose, then on 12^{th}, 24^{th} and 48^{th} week of antiviral therapy. Results. Both HRV and BRS indices decreased after 12 weeks of therapy compared to the initial values; then increased significantly again for the 24th week; and showed further tendencies for improvement at 48^{th} week of therapy. (253±111 at week0 vs.

111.6±81.9* at week12 vs. 183.4±169.6* at week24 vs. 211.6±149.1 ms at week48 for low-frequency HRV index; 8.1±3.9 vs. 5.6±2.0* vs. 8.3±4.1* vs. 8.8±2.9 ms/mmHg for BRS [mean±SEM]; *p<0.05). These trends were independent form presence of cryoglobulins and from virologic response. Sensory function did not change during 48 weeks of therapy. Conclusion. The short term and reversible deterioration of autonomic function at the beginning of anti-HCV therapy may reflect the changes of immune-system caused by immune-mediator interferon. Autonomic dysfunction is known to be associated with impaired immune-function in diseases such as human immunodeficiency virus infection and multiple sclerosis. Further studies are needed, however, to clarify the exact mechanisms.

O-49
Mice carrying a Toll-like receptor 2 mutation on high fat diet show increased accumulation of body fat albeit attenuation of insulin resistance

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Obesity and diabetes are nowadays considered as low-grade systemic inflammatory disorders in which the innate immune system (IIS) might play a relevant role, as suggested by the absence of the metabolic syndrome in *Tlr4*$^{-/-}$ mice subjected to continuous lipopolysaccharide (LPS) infusion. We have recently reported that genetically obese mice experience a drop in intestinal mucosa barrier function leading to leakage of luminal-derived bacterial endotoxins such as LPS in the portal blood that causes hepatic stellate cells activation. In order to investigate whether peptidoglycan fragments, derived from the intestinal microbiota and interacting with the TLR2 of the IIS, can also influence the occurrence of metabolic disorders we allocated 4-weeks-old male C57Bl/6 (WT) and *Tlr2*$^{-/-}$ mice to receive regular chow food (RCF) or very high fat diet (VHFD) for 10 weeks (wks). Body weight was recorded weekly, whereas oral glucose tolerance, fat depots, inflammatory cytokines and PPAR-α levels were

measured at 4, 6 and 10 wks. WT and *Tlr2*$^{-/-}$ mice on RCF showed comparable body weight gain whereas *Tlr2*$^{-/-}$ mice on VHFD were more prone than WT mice to gain weight (32.05±0.5 g and 27.5±0.49 g respectively after 10 wks, $p<0.02$), although no significant differences were observed in food intake among the experimental groups. After 10 wks on VHFD, liver lipid accumulation and abdominal fat depots were more abundant in *Tlr2*$^{-/-}$ as compared to WT mice. Indeed, PPARα level in liver was significantly more up-regulated in *Tlr2*$^{-/-}$ mice on VHFD. However, starting at 6 wks on VHFD, WT mice showed significantly more pronounced glucose intolerance than *Tlr2*$^{-/-}$ mice associated to higher tumor necrosis factor-α and interleukin-1β levels in the liver and blood. In summary, *Tlr2*$^{-/-}$ mice on VHDF exhibit higher body weight gain and fat accumulation but seem to be protected from the occurrence of insulin resistance, suggesting that the TLR2-derived signals influence insulin-activity and weight gain.

O-50
Non-alcoholic steatohepatitis and liver transplantation experience of the University Hospital of Essen

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Nonalcoholic fatty liver disease (NAFLD) is considered to be a hepatic manifestation of metabolic syndrome, which is the most common chronic liver disease in western countries. The clinicopathologic spectrum ranges from simple steatosis through steatohepatitis to end-stage liver disease (cirrhosis) and hepatocellular carcinoma; which is a consistently increasing indication for transplantation. This study aims to report our experience with patients who underwent liver transplantation due to non-alcoholic steatohepatitis (NASH)-related liver cirrhosis. Methods. All deceased and living donor liver transplantations were considered. We ret-

rospectively studied 191 liver transplants between October 2007 and March 2009. Of them, 11 transplants were performed due to nonalcoholic steatohepatitis. Patients' peri-operative course, short- and long-term outcomes were analyzed. Results. 11 were pathologically identified as NASH cirrhosis. There were 3 men and 8 women, ranging in age from 17 to 65 years (mean and median, 50.07 years and 53.03 years, respectively). The median MELD score was 28. The transplanted BMI ranged from 21.1 to 46.1 (mean and median, 31 and 31.36, respectively). After a median (range) follow-up of 63 (0-1430) days, 8 patients are still alive. 3 patients who died had remarkably increased BMI scores in mean of over 30. Conclusion. First, the prevalence of NASH related liver transplantation is permanently increasing in our center. Second, we postulate that liver transplantation in NASH patients is associated with higher mortality and postoperative complications compared to other or alcohol-related transplants. Performing bariatric surgery, e.g. gastric banding, before liver transplantation may improve the outcome in NASH patients.

O-51
Polyphenols partially prevent hepatic steatosis and modulate liver fatty acid composition in rats fed a high fat-high sucrose diet

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Nonalcoholic fatty liver is one of the most common liver diseases in the world. Recent studies demonstrated that resveratrol may prevent against liver lipid accumulation. Nevertheless it is still unknown whether polyphenols modulate liver fatty acid composition. The present study was designed to evaluate the effect of a grape polyphenol (PP) extract on liver lipid content and on fatty acid composition in rats fed a high fat-high sucrose diet. In that aim, 40 male Wistar rats were randomized into five groups of 8 animals: a control group (control) was fed for 12 wk a semipurified diet, a high fat-high sucrose group (HFHS 6wk) was fed for 6 wk a semipurified diet and then for 6 other wk a high fat-high sucrose diet, a

PP group (HFHS+PP 6wk) was fed for 6 wk a semipurified diet and then for 6 other wk a high fat-high sucrose diet plus 0.2% Provinols^{TM}, a high fat-high sucrose group (HFHS 12wk) was fed for 12 wk a high fat-high sucrose diet, a PP group (HFHS+PP 12wk) was fed for 6 wk a high-fat high sucrose diet then for 6 other wk a high-fat high sucrose diet plus 0.2% Provinols^{TM}. Provinol^{TM} is a powder PP extract obtained from red wine that contains 0.15% resveratrol. Liver triglycerides (TG), total cholesterol (TC), free fatty acid (FFA) and phospholipid (PL) content were measured by spectrophometric technique. Liver fatty acid composition was measured after transesterification, by gas chromatography on Silica column. Different lipid classes were separated on thin layer chromatography in order to measure the fatty acid composition of PL, FFA, TG and cholesterol ester (CE). Results demonstrated that PP partially prevent liver TG accumulation in the HFHS+PP 6 wk and HFHS+PP 12wk groups by comparison to rats fed the HFHS corresponding diet, but have no effect on cholesterol accumulation. Moreover they may modulate the fatty acid composition of liver lipid classes by acting on a desaturase enzyme expression and/or activity.

O-52
Evaluation of age-related, different clinicopathological features of patients with resectable hepatocellular carcinoma

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Hypothesis: In hepatocellular carcinoma (HCC) patients with younger ages, the clinicopathological characteristics and long-term postresectional outcomes mandate to be clarified. Design: Case series. Duration of follow up was 528.9 ± 32.1 months. Patients: From a prospective database, 719 HCC patients who underwent hepatectomy were classified into younger group (age <40 yrs) (n = 56), middle aged group (age 40-69 yrs) (n = 482) and elderly group (age >70 yrs) (n = 181). Clinicopathologic factors and postresectional outcomes were compared among these groups based on

the new AJCC/UICC TNM (sixth edition) staging system and the transplantation patient selection criteria. Main Outcome Measures: Clinicopathological characteristics, and postresectional disease-free survivals. Results: The mean age of younger patients was 33.8 ± 5.2 yrs, of middle-aged patients was 58.2 ± 8.6 yrs, and of elderly patients was 74.9 ± 3.6 yrs. Compared to elderly patients, younger patients had less percentage of male, with less history of acute hepatitis, a higher frequency of family history of HCC, a higher frequency of hepatitis B surface antigen positive, a lower frequency of hepatitis C infection, a higher preoperative AFP protein level, and a better preoperative liver function. A significantly higher proportion of younger patients underwent major resection. On pathological examination, younger patients had significantly larger-sized tumors, lower frequency of hepatic steatohepatitis, and more patients in advanced TNM stage III disease. The overall incidence of tumor recurrence was 56.0%, the tumor recurrence rates were comparable in three age groups. Younger patients had significantly higher extrahepatic recurrence rate when compared with elderly patients, 38.7% versus 17.4%, $P < 0.05$. The 5- and 10-year disease-free survival rates in the younger group were 43.0% and 35.5%, respectively, the 5- and 10-year disease-free survival rates in the middle-aged group were 37.2%, and 20.6 %, respectively, the 5- and 10-year disease-free survival rates in the elderly-aged group were 29.5%, and 23.3%, respectively. Younger patients with stage I, II disease had significantly better disease-free survival ($P < 0.05$) than middle-aged and elderly patients. For subgroups of patients with transplantable HCC, the 5-year disease-free survival rates after hepatic resection in younger, middle-aged and elderly patients were 76.7%, 44.0% and 36.4%, respectively. Conclusions: In early stage (TNM stage I, II and transplantable HCC) disease, younger patients had significantly better survivals than elderly ones. The differences in the background factors in relation to tumor progression and detection and surgical factors may be the main reason for the better prognosis. Early detection of small HCC in younger patients is important. For small HCCs originating in both younger and elderly patients, hepatic resection is a reasonable primary treatment associated with favorable 5-year overall and disease-free survivals.

O-53
Conjugated linoleic acid (CLA) fails to reduce steatosis in cachectic tumor-bearing rats

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Cachexia is a syndrome associated with marked changes in lipid metabolism, such as fat accumulation in the liver, reduction of liver LCFA oxidation, and abnormal VLDL secretion. Conjugated Linoleic Acid consists on a group of 28 positional and geometric isomers of linoleic acid and their effect is related with changes in lipid metabolism. Objective: The purpose of this study was to investigate the effect of CLA supplementation upon lipid metabolism and steatosis in tumor-bearing rats. Material and methods: Control (C) and cachectic (TB) rats were divided in three groups supplemented with CLA (CLA), sunflower oil (SF) or water (C) for 14 days. Fat content in the liver was measured as described by Folch, serum cholesterol and TAG levels were determined by enzymatic kits, and APOB and MTP gene expression was evaluated by real time PCR. Results: Fat content in the liver enhanced in TBCLA group when compared with control (CC) and (TB) ($P<0.01$), along with an increased serum TAG content ($P< 0.01$). ApoB and MTP gene expression was lower in TBCLA when compared with control (CC) and cachectic (TB) rats ($P<0,05$). Conclusion: CLA supplementation increases cachexia-associated triacylglycerol accumulation in the liver and plasma. Financial support: FAPESP 08/54091-9

O-54
Personalized rehabilitation approach to Fatty Liver Disease in patients with metabolic syndrome

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Fat liver content increases with the increase of fat mass and insulin resistance. Fatty liver presents a very high prevalence in overweight people and in HIV patients. Dietary energy restriction and exercise increase of energy expenditure are valid tools for therapy, but different somatic and metabolic phenotypes together with different individual psychological attitude to follow protocols make the compliance, the maintainance of beneficial effects, the final results in term of body composition and metabolic control at 1 year unpredictable. Inclusion criteria were: Fatty liver at NMR, increase of ALT, Insulin Resistance (HOMA), increased percentage of Fat-Mass (DEXA), no alcohol consumption. Patient's usual dietary intake and physical activity habit computerized assisted interview data were matched with indirect calorimetry for the evaluation of individual caloric balance. DEXA body compositions, BIA, Forbes equation, basal metabolism were utilized for planning a personalized caloric strategy. Each patient was invited to choose one out the two strategies: reduction of daily caloric intake or an increase an increase of energy expenditure. Make understood of the data may also choose the length of the treatment (3 or 6 months). However, the composition of the usual diet was unchanged if it was not in contrast with haematological parameters, with LARN, and with the composition (carbohydrates 50%, protein 20%, lipids 30%). In the only diet approach group, energy restriction was calculated considering basal metabolism and daily physical activity expenditure. In the exercise group, the planned energy expenditure was calculated considering the need to make negative the metabolic balance in agreement with Forbes equation. Variations in the period basal- 6 months of fat liver content, HOMA, metabolic active mass, ALT, body composition, respiratory quotient were compared in the groups.

O-55
The efficiency of Amaranth oil for correction of oxidative stress and improvement of heart rate variability in patients with type 2 Diabetes mellitus

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Oxidative stress (OS) is known to be an important pathogenetic mechanism of metabolic syndrome and particularly type 2 Diabetes mellitus (DM). This is related to excessive accumulation of oxidative destruction products with slowed redox reactions in cells and tissues. These changes are commonly associated with decreased heart rate variability (HRV) and cardiovascular disorders. Under such circumstances, activation of oxygen-dependent metabolism is essential part of treatment strategy. Mild prooxidant effect can be achieved by supplementation with oil derived from the seeds of Amaranthus cruentus L. (AmO), which consists of predominantly linoleic acid and also tocopherols, tocotrienols, carothenoids, and squalene. We studied the impact of concentrated AmO (1.0 ml per 60 kg of body weight daily for one month) on the OS parameters (levels of TBARS, oxidative modification proteins (OMP), hydroperoxides (HP), LDL-cholesterol, middle mass molecules (MMM), glycosylated hemoglobin (HbA_{1c}), activities of catalase and superoxidedismutase (SOD) in blood) and HRV indexes in patients with moderate and severe type 2 DM. 74 patients aged 51-67 years with disease duration up to 10 years were enrolled. Control group consisted of 35 apparently healthy volunteers of the same age. Severe manifestations of OS were found in all DM patients despite increased activities of catalase and SOD. These biochemical changes were associated with dramatically decreased HRV. Because of wide range of total power (TP) values obtained, the patients were divided into 2 groups, with group 1 including the subjects with low (600-1000ms^2) and group 2 very low (100-600ms^2) TP indexes. Administration of AmO caused activation of aerobic metabolism with significant decrease in TBARS, HP, LDL, and OMP levels, reduction of HbA_{1c} in group 1 patients. Simultaneously, significant increase in most HRV parameters, predominantly due to autonomic upregulation was observed

in this group. The patients with initial low TP values (group 2) demonstrated normalization of antioxidant enzymes activities, however, no changes were observed with initially high levels of TBARS, MMM, and OMP. Notably, marked decrease in HP, LDL, HbA1c was shown in group 2 due to better utilization of these OS markers in redox reactions, which was accompanied by some improvement of HRV parameters. In conclusion, AmO supplementation to patients with type 2 DM improves the intensity of aerobic metabolism by causing mild prooxidant activity. This results in reduction of OS manifestations and increase in HRV. The effect was more prominent in group 1 (with initially higher TP) patients.

O-56
Alcohol toxicity and fatty liver preventive effects of betaine and s-adenosyl methionine

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O-57
The association of metabolic syndrome and food pattern in non-menopause women

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Background and Objective: The metabolic syndrome (MetS) is a cluster of metabolic disorders. MetS is related to prevalence of overweight and obesity and on the other hand is counted as risk factor for cardiovascular disease and type II diabetes. It has been turning to an emerging epidemic in developing countries as well as developed ones. The etiology is a complex interaction between genetic, metabolic, and environmental factors (diet and physical activity), which dietary patterns have attracted the most importance among lifestyle habits. In this study the relationship of food

patterns with Metabolic Syndrome among Tehrani non- menopausal women 18-50 yr was studied. Materials and Methods: Study was conducted as Nested case-control using data from Tehran Lipid Glucose Study (TLGS). Metabolic syndrome was defined according to IDF (International Diabetes Federation) guideline. 18-50 year old non- menopause women were chosen among 12523 individuals participated in TLGS. Subjects who were pregnant, lactating, with hysterectomy surgery, history of cardiovascular diseases, cancer or energy intakes out of 800-5300 Kcal/ day had excluded from the study. Dietary intakes were assessed via 168 item semi- quantitative food frequency questionnaire. Factor analysis, Principal Component Analysis (PCA), was used to derive the dominant food patterns among 920 individuals, those without having any specific diet and awareness of metabolic disorders (hypertension, hyperlipidemia, hyperglycemia and taking medications). In the second stage, 135 cases of MetS were matched to 135 controls for age, and dietary pattern score was calculated for each person in both food patterns in matched groups. Results: Mean age ± SD of subjects was 31 ± 9 years and their BMI was 25.7 ± 5.2 kg/m^2. 14.7% of non- menopausal women had undistinguished metabolic syndrome. Two dietary patterns were identified explaining 23% of the dietary variation in the study. The desirable food pattern was characterized by the consumption of raw vegetables, fruits, starchy vegetables, olive, oiled vegetables, low fat dairy, legumes, nuts, egg, oil, whole grains, fish, high fat dairy and chicken (explained variation 12.07%), and the undesirable food pattern was characterized by the consumption of cola and commercial fruit juice, cookies and sugar, ready foods (sausage and pizza), mayonnaise, snacks (chips and puffed corn), fat, pickle, organ meats, refined grains, meat and salt (explained variation 10.89%). After matching two groups for age, mean ± SD of energy intake, carbohydrate, protein and fat was 2122 ± 591 Kcal/day, 303 ± 103 g/day, 73 ± 24 g/day and 79 ± 31 g/day respectively, and the difference between two groups were non-significant. Adjusting for various confounding variables (energy intakes, energy expenditure, education level, job, family history of diabetes or stroke, smoking and BMI), the desirable food pattern was inversely associated with MetS (odds ratio: 0.87, P-value < .001), and hyperglycemia (odds ratio: 0.34, P-value <0.05). No associations were observed between MetS and undesirable food pattern. Among components of metabolic syndrome (waist circumference, triglyceride,

fasting blood sugar, HDL-cholesterol, systolic and diastolic blood pressure), only triglyceride was associated with this food pattern (odds ratio: 2.17, P-value <0.001). Conclusion: Desirable food pattern including vegetables, fruits, low fat dairy, legumes, nuts, egg, oil and whole grains is significantly associated with reduced metabolic syndrome, whereas undesirable food pattern has no association.

O-58
Life modification treatment of NAFLD in schoolchildren

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Objective: to investigate the effect of lifestyle modifiction on non alcoholic fatty liver disease (NAFLD) of schoolchildren and to study some parameters by which this effect may be influenced. Patients and methods Schoolchildren with NAFLD (112 boys and 51 girls aged 7-18years) were investigated. Before and after two years long non pharmacologic treatment body mass index, blood pressure, serum lipid levels, liver enzyme activities, fasting plasma glucose, insulin, thiobarbituric acid reactive system (TBARS) and total homocysteine (THCy) levels were measured. The NAFLD was detected by ultrasound. Results: NAFLD improved in 71 (43. 6%) patients (responders = group R) and unchanged in 92 schoolchildren (non responders =group NR) after treatment. Increased liver enzyme activity of 8 patients belonging to group R and that of 6 persons from 10 belonging to group NR was normalized after treatment. Before and after treatment mean plasma TBARS levels were 2.9 nmol/ml and 2.1 nmol/ml ($p<0.02$) and mean plasma THCy levels were 17.8 µmol/L and 9.3 µol/L ($p<0.01$) in patients belonging to group R, respectively. In group NR before and after treatment mean plasma TBARS levels were 3.1 nmol/ml and 2.7 nmol/ml ($0.5<p$) and mean plasma THCy levels were 16.3 µmol/ and 14.2 µmol/L ($0,2<p<0.3$), respectively. No other significant differ-

ences were observed between R and NR groups. Consequences: two years long lifestyle modification seems to be useful treatment of NAFLD in schoolchildren in some cases. According to the significant differences found between the group R and NR may suggest the a further antioxidant and vitemin supply for the increase of number of responders.

P-1
Induction of fatty liver by fasting in mouse strain disposed to metabolic syndrome development

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Fatty liver and nonalcoholic fatty liver diseases (NAFLD) have been associated with insulin resistance and are early events in the development of metabolic syndrome. The risk of developing hepatocellular cancer as a consequence of NAFLD was established recently. Fatty liver was observed also in certain physiological conditions like starvation. But the connection between liver fatty infiltration by fasting and predisposition to NAFLD and metabolic syndrome development was not explored. This investigation is an attempt to clear this problem by testing starvation effects in two mouse strains: disposed to obesity, insulin resistance and liver tumor development with age CC57BR/Mv (BR) and insulin sensitive DD/He (DD). Basal blood glucose, insulin and corticosterone levels were higher in 4 month old BR mice. Additionally control animals of BR strain represent higher peroxisome proliferator-activated receptors-α and -γ mRNA levels in liver, than DD ones. Only BR mice demonstrated fatty liver during starvation. Volume of lipid droplets in hepatocytes of these mice increased 10-fold as compared with control values, while DD mice demonstrated decrease in this parameter. Decrease in body weight, blood glucose and insulin levels and increase in blood corticosterone level were observed in fasting animals of both strains. However we observed slow decrease in blood glucose level with simultaneous 2-fold increase in blood urea concentration in DD mice. Contrarily BR strain demonstrated fast decrease in blood glucose level together with 2-fold free fatty acid (FFA) level increase. It may indicate that proteins and carbohydrates are the main energy source in DD mice during starvation, whereas lipids and FFA are responsible for energy production in BR animals accumulating the excess of lipids in the form of liver fatty infiltration. We suppose that starvation leads to fatty liver appearance only in mice which are disposed

to insulin resistance and metabolic syndrome development. The work is supported by grant RFBR 07-04-00864a.

P-2

Association between vitamin D, cardiovascular risk factors and non-alcoholic fatty liver disease (NAFLD) in Italian patients with the metabolic syndrome

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Background and aims. Several studies have demonstrated low serum 25(OH) vitamin D levels in adults with metabolic syndrome (MS) and type2 diabetes, probably due to its insulin-sensitizing action in muscle, adipose tissue and liver. Aim of our study was to investigate the relationship between low levels of vitamin D, metabolic alterations and the presence/degree of hepatic steatosis in MS patients. Methods. 100 consecutive subjects (65 MS and 35 controls) aged from 40 to 70 years were recruited. MS was defined according to ATP-III criteria. Liver ultrasound was performed to diagnose and quantify (I,II and III degree) the presence of NAFLD. Fasting serum 25(OH) vitamin D was measured by colorimetric method. Results. MS patients show significantly lower serum vitamin D levels compared to controls, independently to gender and age (mean±SD: 12.86±7.73 ng/ml *vs* 19.04±8.81 ng/ml, p=0.002), while there are no statistically significant differences between MS patients with or without diabetes. A negative association was observed between serum (25)OH vitamin D levels and the number of MS'components ($p<0.000$). Regression analysis shows that I-degree of steatosis is independently associated with hypovitaminosis D (p=0.04) after controlling for sex,age,diabetes, MS and its individual components. No association was found between serum vitamin D levels and degrees II and III steatosis. 25(OH) vitamin D directly correlates with ALT and AST in MS patients but not in controls (p=0.001, p=0.003). Conclusion. MS patients present reduced serum 25(OH) vitamin D levels compared to controls. Type 2 diabetes does not have an independent effect in determining hypovitaminosis D. After

adjustment for confounding factors, an association between low vitamin D levels and mild fatty liver (but not moderate-severe) has been observed. In addition, our study has shown for the first time that in MS patients relatively-higher levels of vitamin D are associated with a significant increase of transaminases.

P-3

Does the chronic intermittant hypoxia link between obstructive sleep apnea and fetty liver disease?

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Introduction: Currently the common pathogenetic mechanisms in nonalcoholic fatty liver disease (NAFLD) and obstructive sleep apnoea (OSA) are targeted growing attention. The aim of this study is to find out the influence of CIH and OSA related parameters to severity of NAFLD with liver functions tests. Methods: We examined liver functions tests and ultrasonographic data of liver as well as markers of OSA severity (AHI, oxygen desaturation index, nadir oxygen saturation, percentage of time spent with SpO2 < 90% [%T<90]) of 106 subjects. Results: Fatty liver disease was diagnosed in 71 subjects (group-1) and remaining 35 subjects were taken as controls (group-2). As NAFLD severity increased from mild to severe form, mean AHİ and ODI values also increased significantly. Our multivariate analysis showed that AHI, ODI, lowest desaturation values and percentage of sleep duration with SpO2<90 were independent predictors of NAFLD after adjustment for BMI, weight and insulin resistance. Furthermore, the most correlated parameter for the severity of NAFLD was found as the duration of hypoxia. Conclusion: We postulate that sleep fragmentation, or disruption because of frequent hypopnoeic and apnoeic episodes in sleep apnoea patients, may result in elevated levels of pro-inflammatory cytokines that may promote oxidative stress.

P-4

Preventive effect of a melon extract rich in superoxide scavenging activity on obesity, oxidative stress and non alcoholic steatohepatitis in hamsters fed a high fat diet.

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Studies showed that dietary anitoxidants could be a therapy against obesity that is associated with a state of oxidative stress. Thus, we investigated whether a dietary ingredient, a melon juice extract rich in superoxide dismutase, would prevent its development in hamsters. Five groups received a standard diet, or a high fat diet (HF) plus a daily gavage with water (Control) or extract at 0.7, 2.8 or 5.6 mg/day. After 84 days, the higher dose lowered triglyceridemia (68%), lipid and protein oxidation products (35% and 35% respectively), leptinemia (99%) and increased adiponectinemia (29%), leading to a concomitant reduction in insulinemia (39%), insulin resistance (41%) and abdominal lipids (25%). Further, the production of liver superoxide anion was reduced (12%), and the main source of reactive oxygen species production (NADPH and mitochondria) were modified as NADPH-dependent O_2^0-production and mitochondrial maximal activity of cytochrome c oxidase were decreased by the extract. The extract triggered a remarkable decrease of liver lipids (73%) and fully prevented the steatohepatitis induced by HF diet. Chronic consumption of melon extract may represent a new alternative to reduce the obesity induced by a high fat diet. The mechanisms through which it works need to be investigated.

P-5

Liver iron overload in patients with unexplained hyperferritinemia, Impaired Fasting Glucose and liver steatosis

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We measured liver iron overload in 68 subjects, 51 males and 17 females, median age 54.5 years (range 30-78) with unexplained persistent non familial hyperferritinemia.Patients presented the following median values: ferritinemia 674.5 ng/ml (range 239-3532); transferrin saturation 35% (15-50); Serum Glutamic Oxaloacetic Transaminase (SGOT) 25 U/L (range 12-143); Serum Glutamic Pyruvic Transaminase (SGPT) 30 U/L (range 10-98 U/L) and Gamma-Glutamyltranspeptidase (GGT) 36.5 U/L (range 13-641). To evaluate Liver Iron Concentration (LIC) all subjects underwent a biosusceptometric evaluation by Magnetic Iron Detector (MID) with the following results: 48 patients showed no hepatic iron overload; 17 revealed a mild iron overload (LIC 1200-2400 mcg/gr/ww) and 3 a high one (LIC 2700-5000 mcg/gr/ww). These data correlated statistically with hyperferritinemia ($p<0.0001$) and transferrin saturation ($p<0.0001$). Among the patients who performed an abdominal echotomography, 31 showed evidences of hepatic steatosis (grade I: 11 patients; grade II: 17 patients; grade III: 3 patients). Out of these 31 patients, 9 presented a liver iron overload (LIC range 1200-3800 mcg/gr/ww). In these 9 patients we found a significant correlation between hyperferritinemia and Impaired Fasting Glucose (IFG) ($p=0.0039$) and among hyperferritinemia, grade of fatty liver ($p= 0.0003$) and hepatic iron overload ($p=0.0003$). 0ut of these 9 patient, 7 did not meet Metabolic Syndrome criteria following to the Adult Treatment Panel III (ATP III) Guidelines. Therefore our preliminary data suggest that simultaneous unexplained hyperferritinemia, hepatic steatosis and IFG could be related to liver iron overload.

P-6

The relationship between metabolic syndrome components and increased alanine aminotransferase activity

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Background: Nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver disease. It is considered as a hepatic component of metabolic syndrome due to its close relation with hyperglycemia, central obesity, hypertension and dyslipidema. Methods: Retrospective analysis of results from Program of extended preventive care for Czech Army members focused on elevated alanine aminotransferase (ALT) activity and metabolic syndrome components. We enrolled 4.748 career soldiers - 4231 men and 517 women with average age 37.6 ± 7.5 and 36.7 ± 7.2 yrs, respectively. Results: Elevated ALT was in 20 % of men and 2 % of women. In overweight soldiers it was in 22 % of men and 4 % of women and in obese ones in 36 % of men and 10 % of women. Elevated ALT was significantly associated with BMI > 30 kg/m^2 (men - OR 5.6; 95% CI 4.3-7.2 and women OR 9.5; 95% CI 2-44.5), waist circumference >102cm in men (OR 3.9; 95% CI 3.2-4.8), triglycerides > 1.7 mmol/l in men (OR 2.5; 95% CI 2.1-2.9), fasting plasma glucose > 5.6 mmol/l (men - OR 2.1; 95% CI 1.7-2.6 and women - OR 14.2; 95% CI 2.6-77.2). Stronger association was with combination of metabolic syndrome components, BMI and fasting plasma glucose (men - OR 11.3; 95% CI 7.3-17.5 and women - OR 68.2; 95% CI 11-424.2). Conclusion: Occurrence of metabolic syndrome components and mainly its combination are strong predictors of increased ALT activity. It is important to think on NAFLD whenever it is found asymptomatic elevation of ALT particularly if other metabolic disorders such as hyperglycemia, obesity or dyslipidema are present. Supported by MO OFVZ0000502.

P-7
The moderate white wine consumption and the insulin resistance

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The advantageous physiological effect of the wine can be explained partly to the moderate quantity of the alcohol, partly to the polyphenol compounds originating from the grape. The supposed mechanism of the health preventing effect from wine polyphenol components can be the consequence of several biochemical reactions. Their antioxidant and scavenging effect is the first important and mostly examined character.. Aim of the study: We have done a clinical trial in order to know whether the Pintes (an old Hungarian wine) consuming in a moderate quantity has got an effect on the redox state of organism and whether it is able to reduce the insulin resistance in the persons with metabolic syndrome. Ethical permission: TUKEB 69/2000 and 2008. Clinical individuals and methods. 32 persons (26 male and 6 female) took part in the clinical trial. Mean age was 49.7, and 38.7 year, respectively. The examination period lasted for 4 weeks. Among the individuals there were found 7 persons with diabetes (2nd type diabetes mellitus), 25 were treated with hypertension, 14 persons with hyperlipidaemia. The persons included to the study consumed white wine associated to the dinner in the evening. The men consumed 3 dl of wine (alcohol content is 36 g) and the women drank 2 dl wine (alcohol content is 24g). The participants were divided into two groups: 18 persons consumed Pintes wine (2008) and 14 individuals - the control group - drank Rizlingszilvani. Blood tests were carried out at starting and after four weeks at the end of observation. We measured the routine biochemical parameters, the serum lipid concentrations and the parameters characteristic to the redox homeostasis as well as we accounted the HOMA index as well as the QUIKI score showing the insulin resistance. Results: The wine consumption did not influence the body mass index .There were no significant results in the routine biochemical and lipid parameters, but the 4 week wine consumption significantly improved the characteristics of carbohydrate metabolism: The HOMA index significantly decreased

after the consumption of white wine, the QUICKI score increased after the wine drinking period. Conclusions: The consumption of small quantity of white wine is able to decrease the insulin resistance in persons with metabolic syndrome. That is why the modest consumption of wine could be beneficial in health preservation.

The work is closely associated to the EU Project *"COST B35 Action: Lipid Peroxidation Associated Disorders: LPO"*.

We are very greatful to the Veress Vinary for providing the wines for the clinical trial.

P-8

Fatty liver and elevated blood pressure contribute synergistically to the development of metabolic syndrome among non-obese adults

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Background and Aim: Risk assessment for metabolic syndrome (MetS) development among the non-obese adults not yet fulfilling MetS criteria is important in term of primary prevention. The aim of this retrospective cohort study was to assess the risk for MetS development by utilizing two non-invasive indicators sonographic fatty liver (SFL) and elevated blood pressure (EBP). Methods: In both 2002 and 2007, annual health examinations were performed for workers of an electronics manufacturing company. Data of 1330 early-middle-aged (32.3 ± 6.5 y), initially non-obese (waist circumference less than 90 cm for males / 80 cm for females) adults who did not fulfill MetS criteria at baseline were used for final analysis. The health check-ups included personal questionnaires, physical examinations, abdominal sonographic examinations and blood tests. Results: After controlling for baseline confounders, odds ratios of risk factors for new-onset MetS (new-MetS) were: SFL, 2.5 (95% confidence interval (CI): 1.7-3.8) and EBP, 2.7 (95% CI: 1.8-4.2) in total population; SFL, 2.6 (95% CI: 0.9-7.4) and EBP, 6.7 (95% CI: 2.1-21.3) in females; SFL, 2.5

(95% CI: 1.6-3.9) and EBP, 2.4 (95% CI: 1.5-3.8) in males. Synergism test results were: among total population, adults with dual risk factors dramatically raised an 8.0-fold increased risk, SI = 3.5 (95% CI: 1.5–8.2), for new-MetS; female and male adults with dual risk factors raised 43.5-fold (SI = 13.4 (95% CI: 1.4–130)) and 6.7-fold (SI = 3.2, (95% CI: 1.1–9.0)) increased risks, respectively. Conclusions: For non-obese early-middle-aged adults not yet fulfilling MetS criteria, fatty liver and elevated blood pressure are independent of invasive blood tests, and synergistically contribute to the MetS development. We suggest prioritizing these two non-invasive evaluations in the MetS management programs for early-middle-aged non-obese adults.

P-9

Liver regeneration after partial hepatectomy in0 the liver affected by non-alcoholic fattyliver diseae

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Introduction: Non-alcoholic fatty liver disease (NAFLD) is a common hepatic disorder characterized by fat accumulation in the liver in patients who do not drink excessive amounts of alcohol. The liver is the only visceral organ capable of natural regeneration of lost tissue. 2/3 partial hepatectomy (PH) is a well established model for study of liver regeneration. There are several studies of regeneration of the liver affected by NAFLD with inconsistent results. Whereas clarifying the ability of steatotic liver to regenerate is important for decision if the liver affected by NAFLD could be used as a graft for transplantation. The aim of our study was to evaluate whether steatosis affects course of liver regeneration after PH in rats. Materials and Methods: Male Sprague-Dawley rats were fed ad libitum a standard pelleted diet (ST-1, 10% of energy from fat) and high-fat gelled diet (HFGD, 71% of energy from fat) for 6 weeks and then 2/3 liver resection after Higgins and Anderson (1931) was performed. Animals were sacrificed 24 and 48 h after PH; serum ALT, AST, bilirubin, glycaemia, urea, levels of triacylglycerols and cholesterol were measured. Malondialdehyde (MDA) content in the liver (HPLC) and tissue cyto-

kines (ELISA, TNF-alfa, IL-6) were assessed; histopathological samples were prepared (H+E, oil red). The extent of regeneration was evaluated by measurement of liver DNA content and incorporation of bromodeoxyuridine (BrdU). Results and conclusion: Feeding with HFGD caused a decrease in serum ALT ($p<0.05$ 24 h after PH) and urea concentration ($p<0.05$ and $p<0.01$ after 24 resp. 48 h after PH) in comparison with ST-1 group. There were no significant differences among groups in serum cholesterol and glycaemia. HFGD increased production of MDA in the liver 48 h after PH ($p<0.01$). Regeneration of the liver with simple steatosis was not significantly affected as documented by incorporation of BrdU. Supported by MSM 0021620820 and GAČR 305/08/P184.

P-10
Molecular biological changes in alimentary induced fatty liver

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Introduction: Epidemiological studies of the WHO showed that a billion people are overweight and about 400 million people are obese around the world. Obesity is associated with a number of diseases. It is well known, that abnormal morphology and biochemical parameters can be found in obesity and those lead to metabolic syndromes. It was questioned, whether molecular biological changes might be in the background of the morphological and biochemical alterations in cases of fatty liver. Materials and methods: Male Wistar rats (150-200 gbw, in each groups 6 animals) were fed with chow with or without high fat (2% cholesterol, 20% sunflower oil, 0.5% cholic acid were added to the control chow). Redox homeostasis of liver homogenates was examined by parameters of reducing-power, H-donating ability, free SH-groups, total scavenger capacity and dien-conjugate content. Transmethylating ability (bonded HCHO) was measured with OPLC method. Metal and non-metal elements of liver were measured with ICP-OES. The mRNA level of TNFα, iNOS and COX-2 molecular biological factors were measured by Tachman assays. Histolopathological examinations were carried out as well. Results and discussion: Histological preparates showed microvesicluar steatohepato-

sis. Antioxidant levels and transmethylating ability were lowered and free radical reactions were elevated in fatty liver. The levels of toxic metal ions (As, Co, Cr, Mo, Ni, Pb) were higher and essential elements (Mg, P, S, Zn, Fe) were lower in fatty liver. Free radicals and metal elements play an essential role in regulation of signal routes. Oxidative stress, changes of toxic metal element concentrations and diminished methylating capacity caused alterations in NF-κB induced signal transduction routes, which resulted in significant expression of mRNA of TNFα, COX-2 and iNOS proinflammatory factors. Conclusion: Systemic low-grade inflammation can be established in alimentary induced fatty liver.

P-11
A female child involved type 1 Crigler-Najjar syndrome

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Crigler-Najjar syndrome type1 affects less than 200,000 people in the US population and listed as a rare disease by the Office of Rare Diseases (ORD) of the National Institutes of Health (NIH). In present case report, we will try to show the possible complications of the baby if the disease has been mismanaged or referred more lately. 3 months old female baby has been referred to our center due to prolong icterus. She was born in local hospital at April, 29, 2007. Her parents had been recommended for periodic observations after discharge. Unfortunately, she was not seen by any medical expert until the date of admission. We meet her at third month of birth with sever icterus, lethargy, poor feeding and nausea. Primary results of laboratory testes were: total bilirubin 29 mg%, direct bilirubin 4mg%, WBC 8400, reticulocyte 1.5%, PBS and Combs´ test were normal, G6PD was sufficient, sonography of liver, bile ducts were normal. LFT were mildly increased, but liver juice for glucoronile transferase enzyme test was not available in our area so we tried phenobarbital test, without response. Diagnosis of Crigler-Najjar type1 was performed. She was treated by intensive photo therapy and her serum bilirubin level fall down to 9 mg%. She was discharged after 8 days with good general condition, parents were recommended to continue photo therapy and continu-

ous observation at home. She had been candidate for liver transplantation but after several months symptoms of developmental delay were occurred, at present time the surgeon team in Shiraz University have rejected her for liver transplant operation because of her cerebral palsy and floppy baby appearance. Despite of this bitter outcome you can see her sweet smile.

P-12

Prevention of viral-induced liver cancer by myo-inositol, one of the anti-fatty liver food factors

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Myo-Inositol has been known as one of the anti-fatty liver substance in foods, such as rice, beans, etc. Recently, we have found that myo-inositol has potent anti-liver carcinogenesis activity; i.e., oral administration resulted in suppression of spontaneous liver cancer formation in C3H/He male mice. Furthermore, incidence of liver cancer was significantly decreased by administration of myo-inositol together with lactoferrin, and carotenoid mixture. Thus, myo-inositol seems to be useful to protect from various liver diseases.

P-13

The association of obesity with elevated alanine aminotransferase

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Purpose: Recently, several obesity related factors have been identified as risk factors for non alcoholic fatty liver disease (NAFLD) and are also associated with an increase in the risk of hepatocellular carninoma. However, little is known about the relative importance of obesity marker in the association with NAFLD. We thus investigated increased ALT and its association with obesity markers. Subjects and Methods: We measured

ALT in 5,019 Korean adults without a medical history of viral hepatitis, excessive drinking history of alcohol. Anthropometric parameter related obesity and laboratory results were obtained by medical check up program. Results: The average age of increased ALT group was higher than normal ALT group (48.5 vs. 47.4, respectively). All clinical and metabolic variables showed significant differences between subjects with increased ALT group and with normal ALT group (P<0.001). Subjects with increased ALT level also had significantly lower HDL cholesterol (P<0.001). Correlations between increased ALT level and BMI (r=0.216, P<0.001), waist circumference (r=0.197, P<0.001) and triglyceride (r=0.175, P<0.001) was strong positive. Conclusions: These findings suggest that there was positive relationship with increased ALT and obesity related factors.

P-14

Establishment of in vitro model system of hepatic steatosis using hepatocyte

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Nonalcoholic fatty liver disease (NAFLD) is one of the most common hepatic disorders in developed countries. NAFLD progresses through steatohepatitis as an intermediate stage increased liver cell death and hepatic inflammation, and in time is a predominant risk factor for cirrhosis. Generally, animal model system has been used for the study of NAFLD. Here, we investigated the effects of long chain free fatty acids (FFAs) on lipid droplets formation in FL83B (Mouse hepatocyte) and HepG2 cells (Human hepatocarcinoma cell) to establish *in vitro* hepatic steatosis model system. To induce fat-overloading of FL83B and HepG2 cells, cells were incubated with a mixture of different doses of FFAs (Oleate:Palmitate, 2:1 ratio) in DMEM supplemented with 1% BSA for 24 hr. Intracellular lipid accumulation, cytotoxicity and apoptosis in cells exposed to the FFA mixtures were investigated by Nile red staining to detect intracellular lipid droplets, MTS cell viability assay and Western blotting. Lipid droplet fluorescence staining intensity was measured by

fluorescence microscopy and microplate fluorometer (excitation 488 nm and emission 550 nm). Fluorescence microscopy image showed significant increase in the number and size of lipid droplets in HepG2 cells treated with FFAs at 0.5-1 mM, and in FL83B cells treated with FFAs at 0.25-0.5 mM to induce fat-overloading. Furthermore, the lipid droplet fluorescence staining intensity was significantly increased in FL83B cells at 0.25-0.5 mM FFAs. However, MTS assay was shown significant cytotoxic effect in FL83B cells treated with FFAs at 0.5 mM. Therefore, the FFA mixture containing a low dose (0.25 mM) in FL83B cells and a high dose (0.5 mM) in HepG2, is associated with minor toxic and apoptotic effects. These results indicate that FL83B cells are apparently suitable to experimentally investigate the impact of fat over-accumulation in the liver compared to HepG2. These hepatic cellular models may provide a biological basis for clinical findings on dietary patterns and pathogenetic models of *in vitro* hepatic steatosis.

P-15
Comparison of serum anticardiolipin antibodies and carotid intima media thickness in diabetic patients

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Decreased fibrinolytic activity and thrombocyte activation changes are seen in diabetic patients with procoagulant state. In presence of hyperglycemia, the role of anticardiolipin antibodies on phospholipids from the degraded endothelium, and the relation between these antibodies and microvascular and macrovascular complications in diabetic survey are investigated. In our study we aimed to see the relation between Carotid Intima Media Thickness (CIMT) and serum anticardiolipin antibody (ACA) levels and other routine parameters in type I and type II diabetic

patients. Patients were divided into two groups; Group I: Type I DM (n=15) and Group II: Type II DM (n=45). Serum levels of ACA IgG were measured by using ELISA (Trinity Biotech, USA). Mann-Whitney U test was used in statistical analysis. The groups were similar with respect to duration of diabetes (p=0.261). There was no significant difference between ACA levels of two groups. Spot urine microalbumin levels and CIMT were statistically higher in Group II (p=0.0001, p=0.001, respectively). No correlation was found between anticardiolipin antibody and CIMT (p=0.258). Since the patients were elder in the second group and had hypertension and metabolic syndrome, microalbuminuria and CIMT values were higher in this group as expected because of endothelial dysfunction. Large population-based prospective studies are needed to provide stronger evidence about the relation of serum ACA and CIMT in patients with DM.

P-16
Liver histopathology by 100 patients with diabetes type II underwent LSG surgery

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Background: Weight loss in obesity results in marked improvement or resolution of hypertension, diabetes mellitus, and hyperlipidemia. The effect of weight loss on nonalcoholic fatty liver disease (NAFLD) seems to improve the liver function. These results showed spectrum of liver pathology by patients with diabetes type II morbid obesity. Methods: Between February 2003 and December 2008 we performed 100 consecutive sleeve gastrectomy (LSG) operations by diabetes type 2 patients with morbid obesity. LSG was performed as standard procedure. By each procedure were performed preoperative laboratory tests, liver sonography and intraoperative liver biopsy. The improvement of NAFLD was measured by improvement of sonoghrapy and laboratory tests results. Primary outcome measures were improvement and resolution in the 4 components: steatosis, steatohepatitis, fibrosis and cirrhosis. Results: A total count of

100 consecutive patients was evaluated. We found following changes by our patients: 23 steatosis, 50 steatohepatitis, 9 fibrosis and one cirrhosis. In all examined groups with NAFLD the HbA1c level was pathological. Triglycerides were elevated mostly by patients with steatosis hepatis. Lipids pathology progress corresponded with increasing of HbA1c level. Conclusions: NAFLD seems improve in the majority of patients after bariatric surgery-induced weight loss. The severity of diabetes type 2 corresponds with the lipid pathology.

P-17
Liver biopsy in morbidly obese patients

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Background: Nonalcoholic Steatohepatitis (NASH) is a serious condition that is associated to morbid obesity. The rate reported in surgical series is as high as 30%. The diagnosis of the condition should help for a better care of those patients. Methods: In our bariatric program, 184 consecutive patients underwent a surgical liver biopsy (SLB) during a laparoscopic sleeve gastrectomy (LSG) as primary surgery for morbid obesity. The pre operative screening work up included the body mass index (BMI), liver function tests (ALT, AST), HbA1c, cholesterol, triglycerides and liver ultrasonography. Result: Based on the liver biopsy, there were 65 patients with a NASH graded from one to three in the Brunt's classification. There was no complication related to the surgical liver biopsy The ultrasonography has never evocated a NASH. The pre operative laboratory findings ± standard deviation (Sd) are summarized in the table.

	BMI	Mean ALT	Mean AST	HbA1c	Cholesterol	Triglycerides
184 SLB	45.0 ± 6.7	34.2 ± 21.2	22.7 ± 11.9	5.8 ± 1.1	1.95 ± 0.42	1.43 ± 1.00
119 no NASH	43.6 ± 5.7	33.7 ± 21.9	21.1 ± 9.0	5.7 ± 0.9	1.92 ± 0.33	1.40 ± 0.86
65 NASH	45.7 ± 8.7	34.6 ± 17.4	25.3 ± 13.4	5.9 ± 0.9	1.99 ± 0.58	1.43 ± 0.79

Conclusion: Our results confirm that 35.3% of patients with a morbid obesity undergoing a bariatric surgery have a NASH. Although there is a trend for higher BMI, AST, HbA1c associated with a NASH, there is no simple predictive test to rule out this condition in morbidly obese patients. Surgical liver biopsy performed performed as a routine during a LSG for a bariatric purpose is safe and remains the gold standard to establish the diagnosis.

P-18

Characterization of lipid transport in Atlantic cod liver when fasted and fed high or low fat diets

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Atlantic cod deposits dietary lipid mainly in the liver. High-energy diets used in aquaculture, contain high levels of lipids, which often lead to development of fatty livers. In humans, fatty livers may increase the incidence of lipid peroxidation, activate inflammatory signals and initiate apoptosis. This may eventually lead to liver damages. Whether the same problems arise in fish remain to be elucidated. Underlying mechanisms for lipid transport and liver lipid deposition in cod are scarcely studied. The high lipid levels found in cod livers may be caused by a lack of lipoprotein transport out of the liver. We therefore investigated how high (30.5 %) and low (11.4 %) lipid levels in the diet, in addition to fasting affected lipid transport and mobilization in Atlantic cod. The hepatosomatic index (HSI) increased by a factor of 1.5, and the liver lipid index by a factor of 1.7, when fish were fed the high-fat diet. The increase in HSI was mainly due to a larger average size of liver cells, owing to higher levels of lipid deposition than in the livers of fish fed the low-fat diet. In fish from the high-fat dietary group, however, vesicles with the size of VLDLs were found in liver cells. When the fish had been fasted, these particles were not present in the tissues. High density lipoprotein (HDL) was the predominant lipoprotein class in cod serum, followed by low density lipo-

protein (LDL). Some VLDLs and chylomicrons were also present in the serum. There was a tendency to reduced liver lipid index in fasted cod, indicating lipid mobilization from the liver. An increased degree of blood capillary vascularisation (angiogenesis) was seen after fasting, this is likely a mechanism to improve the supply of nutrients and FAs from the liver to other tissues. Our results show that VLDL secretion is limited, but do exist. Hence, lack of these proteins is not the sole reason for liver lipid accumulation.

P-19

AMP deaminase and adenosine deaminase are activated in ammonia intoxication and hepatitis

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Cytosolic enzymes AMP deaminase and adenosine deaminase catalyze AMP and adenosine deamination. Two enzyme reactions constitute rate-limiting steps of adenine nucleotide catabolism and play important roles in cellular energy metabolism. Decrease in intracellular ATP contents can be a consequence of adenylate breakdown as a result of parallel triggering both AMP deaminase and adenosine deaminase reactions. Such the hypothesis was not tested up to now. As the impairment of energy metabolism contributes similarly to the failure of fatty liver, carbon tetrachloride (CCl_4)- and ammonia-intoxicated livers and to hepatic encephalopathy, we aimed to determine whether liver dysfunction affects activities of AMP deaminase and adenosine deaminase in rat liver and brain tissues. In this study the effects of acute ammonia intoxication and subacute CCl_4-induced hepatitis on the enzyme activities in cytosolic fractions of rat liver, neocortex, cerebellum, striatum and hippocampus were investigated. Activities of both AMP deaminase and adenosine deaminase in the liver were shown to be elevated by 2.4-4.2-fold ($P < 0.0001$) in both models of hepatic deficiency as compared with controls. In acute hyperammonemia activities of AMP deaminase and ADA increased by 46-59% ($P <$

0.02) in the neocortex and did not change in the striatum. In the hippocampus of hyperammonemic rats, only AMP deaminase activity was increased by 48% ($P = 0.0004$) and in the cerebellum, only ADA activity was increased slightly but significantly (by 26%, $P < 0.05$). Results suggested that two parallel pathways of AMP breakdown, including AMP deaminase and ADA reactions, respectively, are up-regulated simultaneously, probably in order to ensure prompt and effective depletion of adenylate pool of liver and selected brain regions. It is expected that similar changes can occur in other liver diseases such as fatty liver, cirrhosis and hepatic encephalopathy and in other tissues. The level of activation of each of two enzymes under pathological conditions seems to be tissue specific and ranged from 0% to at least 320%. These changes are likely to occur in cells preprogrammed to die.

P-20

Is the rat liver affected by non-alcoholic steatosis more susceptible to toxic effect of thioacetamide?

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Introduction: Non-alcoholic fatty liver disease (NAFLD) is an important cause of liver-related morbidity and mortality. Primary NAFLD is thought to be the hepatic manifestation of the metabolic syndrome. There is only little evidence about altered sensitivity of steatotic liver to toxic injury. Aim: The aim of this project was to test whether hepatic steatosis sensitizes rat liver to acute toxic injury induced by thioacetamide (TAA). Materials and Methods: Male Sprague-Dawley rats were fed ad libitum a standard pelleted diet (ST-1, 10% of energy from fat) and high-fat gelled diet (HFGD, 71% of energy from fat) for 6 weeks and then TAA was applied intraperitoneally in one dose of 100 mg/kg. Animals were sacrificed in 24, 48 and 72 hours after TAA administration and serum activities of ALT and AST, total bilirubin and glycaemia were measured. Respiration of isolated liver mitochondria was assessed using high-resolution respirometry (Oroboros 2k). Malondialdehyde content in the liver (HPLC) and tissue and serum cytokines (ELISA, TNF-alpha, IL-6, TGF-

beta-1) were measured and histopathological samples were prepared (H+E, bromodeoxyuridine (BrdU) incorporation). Results: Activities of ALT after 48 h ($p<0.01$) and AST after 24 and 48 h ($p<0.001$) and serum total bilirubin after 48 h ($p<0.01$) were significantly higher in HFGD group after application of TAA in comparison with ST-1. There were no differences between corresponding groups in respiration of isolated mitochondria. Serum TNF-alpha after 24 and 48 h ($p<0.01$ and $p<0.001$, resp.), liver tissue IL-6 after 72 h ($p<0.001$) and TGF-beta-1 after 24 and 48 h ($p<0.001$) were elevated in TAA-administrated rats fed by HFGD. Centrilobular necrosis and inflammation and incorporation of BrdU after TAA treatment were more pronounced in HFGD in comparison with animals fed by ST-1. Conclusion: Liver affected by NAFLD, in comparison with nonsteatotic liver, is more sensitive to toxic effect of thioacetamide. Supported by MSM 0021620820 and GAČR 305/08/P184.

P-21
Determination of severity of hepatic steatosis in chronic hepatitis C by computer-assisted morphometric image analysis-correlation with clinical data and treatment response

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Introduction: Hepatitis C (HCV) is a common cause of chronic liver disease with some potential for progression to cirrhosis. Steatosis is present in almost 50% of patients infected by HCV. Hepatic steatosis can be related to host factors (obesity, metabolic syndrome or insulin resistance) or to the genotype of virus (HCV genotype 3). Hepatic steatosis affects the response rate to the antiviral therapy and it is associated with liver disease progression. Aim: Our aim was to investigate the severity of steatosis in connection with chronic HCV hepatitis as well as with the treatment response. Patients and methods: 10 anti-HCV- and HCV-RNS-positive patients with chronic hepatitis were enrolled (male: 2, female: 8, age: 53±3.6, BMI: 25.51±3.085 kg/m², grade: 4.8/18±1.686, stage: 2.7/6± 1.33. The other etiological factors of chronic hepatitis were excluded. The severity of steatosis in pretreatment liver biopsy was determined by a

computer-assisted morphometric image analysis in addition with routine histological grading. The demographical data, liver enzyme activities as well as treatment response were compared with the severity of steatosis. Results: The mean severity of steatosis was 15.68±5.590%. There was no significant correlation with the severity of steatosis and biochemical response. Conclusions: Mild hepatitis steatosis was determined in every chronic HCV hepatitis. Further studies are needed for the investigation of the connection between steatosis and treatment response.

P-22

Effects of atorvastatin on progression-regression of steatohepatitis in hyperlipidemic chickens

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Introduction: Nonalcoholic fatty liver disease (NAFLD) is now recognized as the hepatic manifestation of the metabolic syndrome affecting up 70% of patients with metabolic syndrome and elevation of aminotrasnferases. Histological features of NAFLD include steatosis, lobular inflammation, hepatocellular ballooning, Mallory´s hyaline and even the fibrosis appearance. Aims & Methods: The aim of the present study was to determinate the effect of diet and atorvastatin on NAFLD induced by hyperlipidemic diet in experimental animals. We carried out serum biochemical analysis and histological quantifications by means of an image analysis system and the NAFLD activity score (NAS) was obtained. We used one-hundred white Leghorn chickens which were randomly assigned to 2 Kinds of diet: a standard diet and a hyperlipidemic diet. Afterwards the chickens fed on hyperlipidemic diet were divided in four groups (three-month period) with different diets. Thus, the groups of our study were as follows: group A (healthy control); group B (hyperlipidemic progression

goup); group C (spontaneous regression group); group D (pharmacological regression group) and group E (pharmacological progression group). Results: We observed that the hyperlipidemic diet reproduces the key features of human NAFLD. The control hyperlipidemic (B) had significantly higher levels of total cholesterol and tryglicerides than other groups. The removal diet and/or atorvastatin treatment decreased the steatosis, inflammation and hepatocellular lesion grade in the liver. We have observed a greater disease´s activity in progression groups (B, E) than regression groups (C,D) and lower activity in the treatment groups (E, D) with regard to non-treated groups (B, C). The image analysis of histological features (steatosis and inflammation) has a good reproducibility and precision. Conclusion: In conclusion the suspension of the hyperlipidemic diet and/or atorvastatin treatment has a positive effect on our chicken experimental model.

P-23

Steatohepatitis mediated by hepatitis C virus core protein is ameliorated by blocking complement activation

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The pathogenesis of inflammation and fibrosis in chronic hepatitis C virus (HCV) infection remains unclear. Transgenic mice with constitutive HCV core over-expression display steatosis only. However, core protein production in these models begins during gestation, in contrast to human hepatitis C virus infection where protein production occurs post-natally and typically in adults. To more realistically model the effect of core protein production in the adult liver, a mouse with conditional expression of HCV core was developed and the effect of core protein production in the adult liver examined. Liver biopsy samples from transgenic mice with tetracycline(tet)-regulated conditional core protein expression were evaluated immunohistologically. Microarray analysis of HCV transgenic mice with steatohepatitis pointed to a role of the complement pathway. This was further explored by blocking complement activation by in vivo administration of CD55 (decay accelerating factor for complement), which inhibits

activation of C3. Transgenic mice exhibited low, intermediate, or high HCV core protein expression when fed a permissive diet of standard chow. Asides from hepatic steatosis, hepatic inflammation and fibrosis were coincident with intermediate levels of core protein. Microarray analyses of inflamed liver demonstrated activation of both the complement (C3 up-regulation) and coagulation pathways (fibrinogen B up-regulation). Administration of CD55 reduced hepatic inflammation. Transgenic mice that conditionally express intermediate HCV core protein develop inflammation, steatosis, and fibrosis. These effects mediated by HCV core are reduced by administrating CD55, a regulator of the complement pathway. The model may be valuable in investigating the pathogenesis of liver inflammation in chronic hepatitis C.

P-24

Curative effect of extracts of *Sapindus mukorossi* and *Rheum emodi* in CCl4 induced liver cirrhosis in male rats

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Aim: To study the curative effect of Sapindus mukorossi and Rheum emodi extracts in CCl4 induced liver cirrhosis in male rats. Methods: The dried powder of S. mukorossi & R. emodi was extracted successively with petroleum ether, benzene, chloroform and ethanol and concentrated in vacuum. The curative effect of the extracts of the fruit pericarp of S. mukorossi and rhizomes of R. emodi was studied using CCl4 induced liver cirrhosis in male rats. Results: Extracts of the fruit pericarp of S. mukorossi (2.5mg/mL) and rhizomes of R. emodi (3.0mg/mL) protected the rats from CCl4 induced liver cirrhosis as judged from histopathological evidences and serum marker enzyme activities. Conclusion: We can conclude from this study, that the extracts' of S. mukorossi and R. emodi can cure the CCl4 induced liver cirrhosis in male rats.

P-25
Genetic polymorphisms of the Peroxisome proliferator-activated receptor γ (PPAR γ) and Leptin receptor gene in patients with Non-Alcoholic Fatty Liver Disease (NAFLD)

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Introduction: NAFLD refers to a wide spectrum of liver diseases ranging from simple fatty liver (steatosis), to nonalcoholic steatohepatitis (NASH), to cirrhosis. PPARγ and the leptin receptors play an important role in lipid metabolism, adipogenesis, inflammatory and also in fibrogenic signalling, where leptin has a profibrotic, PPARγ an antifibrogen effect. Aims: In the present study, we tested the occurrence of the Pro12Ala mutation of the PPARγ gene and the Q223R mutation of the leptin receptor in patients with NAFLD. Methods: 235 liver biopsies from patients with NAFLD were monitored and categorized according to Kleiner et al. (Hepatology 2005) in comparison to 105 alcoholic fatty liver disease (AFLD) biopsies. DNA were extracted, and taken for single nucleotide polymorphism (SNP) analyses by Real Time PCR using locked nucleic acid (LNA) probes. Further, 200 DNA samples of healthy blood donors were taken as a control. Results: In the control, the NAFLD 22% of cases showed heterozygous and 2% homozygous occurrence of the Ala12-PPAR γ 2 allele. However, in biopsies of NAFLD patients, carrying the Ala12 allele, less ballooning was observed and in the groups with progressive fibrosis of grade S2 to S4, the Ala12 mutation appears more often than in patients with no or moderate fibrosis. The overall distribution of homo- and heterozygous Q223R mutation of the leptin receptor in patients with NAFLD and AFLD corresponds to the pattern found in the control collective of blood donors. Conclusion: Incidence of Pro12Ala mutation in the PPARγ2 gene suggests that the Ala12 substitution might be involved in bivalent functions: impaired fat accumulation on one hand, and in promotion of steatohepatitis and fibrosis on the other.

P-26
Metabolic changes in hepatocytes from rats on raw soybean diet

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Background and aims: A high level of dietary fat intake is believed to be a major factor in the development of obesity and insulin resistance. We showed that low carbohydrate /high n-6 polyunsaturated fatty acids (PUFA) diet causes the development of insulin resistance, without development of obesity. The aim of this study was to determine metabolic changes and insulin effects in vivo and in vitro in rats fed three weeks with raw soybean containing high level n-6 and n-3 PUFA. Materials and methods: Hepatocytes were isolated by a collagenase perfusion technique and cultured for 24 h. ^{14}C-U-glucose incorporation in glycogen, alfa-amino^{14}C-isobutyric acid (AIB) transport and glucose production was measured in cultured hepatocytes. Results: Body weight was approximately 30% lower in rats on the raw soybean diet. Intravenous glucose tolerance test was normal. Basal glucose production was 50% higher in hepatocytes isolated from rats on a raw soybean diet than in those on standard diet. The glucagon 146 % increased glucose production in hepatocytes from rats on standard diet. Glucagon effect was 86 % higher in hepatocytes from rats on raw soybean versus standard-fed animals. Insulin did not decrease basal or glucagon-stimulated glucose production. In hepatocytes obtained from rats on standard diet insulin produced more 100% increase of glucose incorporation in glycogen. In rats on raw soybean diet basic glucose incorporation was very low and insulin did not change rate of glucose incorporation. In hepatocytes obtained from rats on standard diet insulin produced 80% increase of AIB transport. In hepatocytes obtained from rats on raw soybean diet basic AIB transport was 37% higher, but insulin effect was strongly reduced. Conclusion: These results clearly demonstrate that altering the macronutrient proportion of the standard diet from high carbohydrate/low fat to high n-6, n-3 PUFA/ low carbohydrate diet causes the development of insulin resistance with negative energy balance.

P-27
MicroRNAs: Potential therapeutic targets for metabolic syndrome, a predictor of fatty liver

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Metabolic syndrome (MS) is a constellation of manifestations including central obesity, glucose abnormalities, dyslipidemia and hypertension. A quarter of the world's adults have MS with the majority living in Asia. Fatty liver is a hepatic condition in MS. Large proportion of individuals with MS develops fatty liver over time; hence MS can serve as a predictor of fatty liver. MicroRNAs (miRNA) are short noncoding RNAs that regulate 30% of protein-coding genes. The emerging field of miRNAs has revealed its potential roles in the diagnosis, prognosis and therapy of MS. In this study, we seek to understand the miRNA-mediated molecular events in MS development. Two hundred subjects were screened for this study and those with metabolic disorders were identified based on the National Cholesterol Education Program criteria. All subjects were males with a mean age of 46.2 ± 5.7 years. The ethnic distribution consisted of Chinese, Malays and Indians. Total RNA was fractionated and tagged with Hy3 fluorescent dye followed by overnight hybridization on miRCURY LNA™ microarray chip for miRNA profiling. Significant differences were observed between the miRNA profiles of healthy individuals and subjects with MS, who exhibited dysregulated miRNA expression. Our study has shown that miRNA profiling could prove to be a useful tool in understanding the molecular events and pathogenesis of MS, with a potential to serve as early biomarkers as well as therapeutic targets for fatty liver. This work has been supported by a NMRC grant from EDG08may017, Singapore.

P-28
Quantitative diagnostic system for abdominal palpation

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The metabolic syndrome has become one of the major public-health challenges worldwide. Metabolic syndrome develops because of an accumulation of intra-abdominal fat. Abdominal palpation is commonly performed for the diagnosis of diseases and metabolic syndrome. The abdominal palpation is noninvasive, quick and small in cost technique because it is performed only by hand without any medical equipment. However, the issue of this technique is less-accurate, poorly-reproducible and to need a massive experience of doctors because sense of touch is always told intuitively by senior doctor or text book. Therefore, it is required to develop a quantitative measurement system. In this research, we propose a measurement system to measure an elastic force of abdominal surface where doctors examine. We developed the prototype of measurement system by utilizing haptic device, Omega.3 (Force Dimension Inc.) which presents information on the feeling and the sense of touch when the operator comes in contact with the object in the computational virtual space. Although it is normally used as the input device for the virtual reality-based simulation, we found that it is also possible to use as the measurement system because of high spatial resolution and large continuous force. At the beginning of this study, we evaluated the accuracy in comparison with conventional load-cell device, and confirmed that it has sufficient reliability. In the field of oriental medicine, a symptom called "Shofukufujin" is one of the basic symptoms. This symptom makes the center point of infraumbilical area softer than the around area, and gives an indication of diabetes, subvirile condition and so on. It is verified that the proposed measurement system can automatically distinct the hardness of that point for 10 healthy subjects and we confirmed high correlation between the output of the system and diagnosis of experienced medical doctor.

P-29

Amaranth oil impact on improvement of metabolic parameters in adult patients with diabetes type 2

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We studied metabolic parameters in diabetes type 2 patients following amaranth oil diet. Cold-pressed non-raffinated amaranth oil enriched in unsaturated fatty acids, tocothrienol and squalene that affect lipid and carbohydrate metabolism was provided by LLC "Russian Olive".44 diabetes type 2 patients (34 females and 10 males) with arterial hypertension (AH) were randomly assigned into two groups: 1) control group with traditional therapy and standard diet (22 subjects) and 2) basic group with traditional therapy and amaranth oil diet (22 subjects) who received 10 ml of amaranth oil daily during 14 days. Average age for enrolled patients was 57.48±1.39. Diabetes was diagnosed for 8.26±0.61 years and AH was manifested for 8.82±0.68 years. Statistically significant improvement of triglyceride (TG) level from 2.59 to 1.73 mM/L was observed in basic group while TG level as 2.44 – 2.47 mM/L was detected in control group. Total cholesterol level dropped from 5.83 to 5.23 mM/L and low-density lipoprotein cholesterol (LDL-C) level decreased from 3.63 to 3.5 mM/L in basic group only. The normalization of glycated hemoglobin (HbA1) was progressive in basic group. Atherogenic Index of Plasma (AIP) decreased from 5.03 to 4.74. Glycemia parameters were being decreased in 8, 11, 13, 17 and 21 hours after amaranth oil administration. Carbohydrate and lipid metabolism parameters' analysis demonstrated that amaranth oil-containing diet positively influenced TG level, diastolic blood pressure and pre-prandial glycemia in 8 and 13 hours. Therefore, amaranth oil-containing diet leads to improvement of diabetic dyslipidemia and carbohydrate metabolism of diabetes type 2 patients.

P-30

Melatonin prevents oxidative DNA damage in non-alcoholic steatohepatitis: an experimental study

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Nonalcoholic steatohepatitis (NASH) may progress to advanced fibrosis and cirrhosis. Oxidative stress is one of the important pathophysiological mechanisms in NASH. Melatonin is a potent antioxidant. We aimed to evaluate the effects of melatonin on NASH in rats. NASH was induced with methionine and choline-deficient diet (MCDD) in rats. Thirty-four male Wistar rats were divided into four groups. MCDD group (n=8), MCDD+melatonin (50 mg/kg/day intraperitoneally) group (n=8), control diet group (n=10) and control diet+melatonin (50 mg/kg/day intraperitoneally) group (n=8). Colorimetric methods were used to determine the level of the oxidative stress markers [MDA (malondialdehyte), PCO (protein carbonylation], except 8-hydroxy-2'-deoxyguanosine (OHdG), which was measured by ELISA. MDA, PCO and 8-OHdG levels in the plasma of MCDD group were higher than controls and melatonin treatment significantly reduced these parameters according to MCDD group. We observed no harmful effects of melatonin. The present study suggests that melatonin could reduce DNA damage by reducing oxidative stress in NASH.

P-31
Primary human omega-6 and omega-3 ratio intake improvement by animal dietary adjustment

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Research indicates that omega-3 polyunsaturated fatty acids help prevent risk factors associated with number of chronic, cardiovascular diseases and inflammation. Omega-3 efficacy is mediated through interactions with omega-6, that makes important to maintain an appropriate balance of omega-3 and omega-6 in the diet. Addition of oils rich in omega-3 to laying hens feed with omega-6:omega-3 primary ratio 9:1 to 3.4:1 by fish oil and 1:1 by flax seed oil were adjusted. Feed by vitamin E in 2 mg/g polyunsaturated fatty acids effectively amount as an antioxidant was enriched. Feed oil increment resulted in significant increase of blood high density lipoproteins, eicosapentaenoic, docosahexaenoic and α–linolenic acids concentrations and decrease in arachidonic acid concentrations in comparison to the control group. Significant increase in omega-3 levels in treatment groups in fatty tissue were observed, too. More concretely, addition of flax seed oil gave fivefold and fish oil about eightfold rise. Although omega-6 levels were 50% elevated at once, omega-6:omega-3 ratios under 1,8:1 in both treatment groups were markedly decreased. Similar results in eggs from 0,75% in control group to 11,24% (flax seed oil) and 12,98% (fish oil) omega-3 content enhancement were obtained. Omega-6:omega-3 ratios from 14,36 in control group to 1,4 (flax seed oil) and 1,3 (fish oil) positively relapsed. Current results showed omega-3 feed addition to be prospective solution for poultry products omega-3 levels increase. Poultry products represent inconsiderable mass of human diet. Such improvement could eventuate in increased human intake and prevent civilization diseases issued from wrong omega-6:omega-3 ratio.

P-32
A nano-functionalized real-time electrochemiluminescent biosensor for alanine transaminase assay

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The level of alanine transaminase (ALT) is an index of liver function. While the liver was damaged, ALT would be released to serum for up to 50 folds. Serum ALT has been identified as the standard biomarker for liver injury in diagnosis. We developed an electrochemiluminescent (ECL) biosensor for ALT assay based on its bio-recognition and enzymatic catalysis combined with pyruvate oxidase (PYOD). The potassium ferricyanide was adopted as activator and carbon nanotubes functionalized platinum was used as basal electrode. The ALT catalyzes L-alanine and α-ketoglutarate to produce pyruvic acid which could be further enzymatically oxidized by PYOD to yield H_2O_2 to intensify the ECL of luminol. The biosensor showed excellent characters for real-time assay of ALT under room temperature, as linear response in the concentration range from 0.00475 to 350 U /L (r= 0.993), and the relative standard deviation of 2.5% (C_{ALT} = 47.5U/L, n = 6). The biosensor was applied to assay the ALT level in rat serum with average recovery of 90.5%. The interferences of possible coexisted substances were evaluated by analyzing a standard solution of ALT (4.75U/L) with interferential tolerance limit of 10%. It could be ensured by experimental results there were no interferences for 5.45×10^{-5}mol/L of ascorbic acid, 3×10^{-6}mol/L of uric acid, 5.58×10^{-5}mol/L of lactic acid, 3.57×10^{-5}mol/L of choline, 1.63×10^{-5}mol/L of dopamine, and maximal 0.2g/L of K^+, Na^+, Mg^{2+} and Cu^{2+}. Heparin sodium which was used as anticoagulant for sampling has also no interference to the determination.

P-33
Effects of PFOs on Carassius Aurats and kinetics models

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This study investigated the effects of perfluorooctane sulfonate (PFOs) exposure for varying durations and at multiple concentrations to *carassius aurats* on tissues and organ (plasma, liver, kidney, muscle and brain) and reproductive hormone (plasma testosterone, 11-ketotestoterone, 17β-estradiol) and cell performance (membrane fluidity and potential) as well as kinetics models. The results showed that plasma PFOs concentrations were higher than those in other tissues, brains presented significantly lower PFOs concentrations than in other tissues, different ranking of mean tissue concentrations: plasma, liver, kidney, muscle, brain. PFOs caused significant decrease in serum cholesterol levels compared to control levels ($p<0.05$). No significant differences in serum cholesterol concentration of male and female *carassius aurats* ($p>0.05$). Continuous incubation time induced a further decrease in serum cholesterol in *carassius aurats*, Circulating testosterone were significantly depressed in male *carassius aurats* with the increased PFOS concentration exposure. PFOs into serum of male *carassius aurats* present a time- and dose-dependent manner, but no significant differences in female *carassius aurats* with the increased PFOs concentration exposure ($p < 0.05$). Circulating 11-ketotestosterone titers were significantly depressed in male *carassius aurats* compared to control levels ($p=0.018$), and *carassius aurats* exposed to 1.0, 1.5, 2.0, 2.5 and 3.0 mg/L PFOs for 16 had reduced testosterone levels in males ($p_{ANOVA}=0.005$) but no changes in females. Circulating 17β-estradiol titers in *carassius aurats* were reduced with the increased PFOs concentration. Exposure to PFOs significantly increased membrane fluidity of *carassius aurats* leukocytes, the membrane fluidity was determined to be dose-dependent. The highest dose PFOs significantly different ($p=0.05$) compared to the lowest concentration to cause effects on membrane potential. Serum PFOs concentrations in males *carassius aurats* steady state concentration during the study and that

PFOs had a relatively short residence time in serum with half-lives of 38.5 and 34.3 days for male and female *carassius aurats,* respectively.

P-34

Quantitative evaluation method of diffuse liver diseases based on characteristics analysis of echo signal

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B-mode ultrasound imaging is highly sensitive to changes in the acoustic properties and structures of tissues. We proposed a quantitative evaluation method of the degree of advance of diffuse liver diseases such as fatty liver and fibrosis using the statistical characteristics analysis of the echo signal. We sampled radiofrequency signals in rats and patients by ultrasonic diagnostic equipment, including some with normal livers, and compared them with the pathologic fatty/fibrosis grade determined at examination of biopsy specimens. The degree of deviation of the statistical characteristic of the echo signal from an ideal homogeneous medium case was calculated by the combination of some analysis parameters in our statistical analysis method. The statistics of the echo amplitudes in a normal liver fitted the Rayleigh probability density function (PDF), because normal liver parenchyma is mainly composed of a 3D arrangement of many structures smaller than the wavelength of the typical ultrasound pulse used in clinical examinations. The PDF of the echoes did not, however, fit the Rayleigh PDF in livers that contain fibrosis, including cirrhotic livers, because the nodules and fibrous structures that develop are larger than the ultrasound wavelength. In a fatty liver, the high echo from lipids hides structures such as small blood vessels, and RDF was approximated to the Rayleigh PDF more than a normal liver. Furthermore, change of analysis parameters at the time of changing the size of a region of interest of analysis differed from the case of normal liver. In the comparison result between statistical analysis results and pathological images, it was confirmed that some analysis parameters change depending on the size of the scatterer in liver, and others change depending on the scatterer density. These results show that the liver tissue change could be evaluated by statistical analysis of echo signal.

P-35
Details of special diets and additional information

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P-36
From steatosis to steatohepatitis: is there any early diagnostic marker?

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Nonalcoholic fatty liver disease (NAFLD) accounts to a wide spectrum of liver damage that ranges from simple steatosis to steatohepatitis and subsequent progression to advanced fibrosis and finally cirrhosis. Several predisposing factors have been related to NAFLD such as obesity, diabetes, dyslipidemia, drugs and parenteral nutrition. However, the pathogenesis of NAFLD and its progression to fibrosis and chronic liver disease remains still unknown. Being asymptomatic, fatty liver is often undetected, and since there is no accurate laboratory diagnostic tool for it, the disease is either detected by chance when the patient is subjected to abdominal scanning examination or when steatohepatitis takes place and signs of the disease as well as alteration in blood parameters begin to appear which makes the treatment efficiency highly limited. The current study was carried out to follow up the disease progression by broad screening measurements in order to discover a new biomarker that can help early detection and diagnosis. Moreover, we also investigated the

secondary complications of hepatic failure on the nervous system and incidence of neuro-disorders by measuring neurotransmitters catabolic enzymes activities as an index of the neurotransmitters level. Liver damage was induced in rats by intraperitoneal injections of Carbon tetrachloride (CCl4) with a dose of 20µl/kg three times a week for 4 weeks. pro-oxidants/ antioxidants status, status of insulin resistance, inflammatory markers and energy producing enzymes at biochemical level (colorimetric, spectroscopy and ELISA techniques), protein profile and DNA expression (qPCR) were assayed. Results were supported by histopathological examination of the liver.

P-37

Morphological features of adjournment lipid granules at patients with chronic hepatitis C and opioid drug addiction

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The aim of our research became research of electronically-microscopic features of adjournment lipid granules at patients with chronic hepatitis C (CHC) and opioid drug addiction (ODA) with steatosis. Under supervision there were 15 CHC with ODA patients in the age of 22 - 34 years, 12 men and 3 - women. Diagnosis of CHC has been established on the basis of a complex of clinico-biochemical parameters, proved to be true by definition of antibodies-anti-HCV and polimerasis chain reaction - HCV-RNA. It has been established, that in many hepatocytes, mainly, of 3-rd zone are observed numerous vacuoles of fats which have the different sizes, from small-sized granular up to large granular and different electronic density. In hepatocytes fatty drops can freely be in cytoplasm or in tanks of endoplasmatic netting. In a significant amount of hepatocytes, dense lipid vacuoles borrow the majority of cytoplasm, displace organellas, deform a kernel of a cell, have contact with mitochondrions. In a place of this contact mitochondrions get attributes of damage of the superficial membrane. At expressed steatosis in sinusoids in a zone of contact of hepatocytes with lymphomonocytic infiltrate, substantial growth of destructively changed organelles of hepatocytes, lipid granules, significant activation of Kupfer cells (swelling of kernels, separation of KC

from a wall a sinusoid, activation of phagocytosis), disappearance from cells ITO granules, their transformation in fibroblasts is observed. Mature fibroblasts have expressed granular endoplasmatic reticulum, the developed lamellar complex, elements contracted filaments, takes place expressed perisinusoid and pericellular fibrosis with adjournment of dense bunches fibrils.

P-38
Profiles of ALT in male subjects with sonographic fatty liver carrying serum HBsAg

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Objectives: To investigate the clinical characteristics of HBsAg positive subjects diagnosed as fatty liver with B ultrasonography (SFL). Methods: Subjects attended the routine health examinations held from June to September 2006 in our hospital. All subjects were in range of 18 to 70 years old and without severe diseases. Data including gender, ages, height and body weight, and fasting plasma glucose, serum triglycerides, total and subtypes of cholesterol, ALT, AST, HBsAg and abdominal sonographic evaluations. Results: Prevalence of HBsAg positive SFL (sAg^+/SFL^+) was 2.24% (100/4469), and SFL occurred in HBsAg carriers (n=547) with a lower ratios (18.3% vs 24.0%, p=0.003) than in those without HBsAg (n=3922). All male subjects (n=3224) were then analyzed. Proportions of ages >40, body mass index >25, elevated plasma glucose, elevated cholesterol and elevated ALT (>40 IU/L) in (sAg^+/SFL^+, n=94) were similar to HBsAg negative SFL (sAg^-/SFL^+, n=837) but significantly higher than those in HBsAg carriers without SFL (sAg^+/SFL^-, n=318) or subjects without either HBsAg or SFL (sAg^-/SFL^-, n=1975). sAg^+/SFL^+ subjects had the higher risks having ALT levels over 60 IU/L (OR=6.341, 95% CI=3.596-11.180, p<0.001) compared to sAg^-/SFL^+ (OR=4.234, 95% CI=3.020-5.937, p<0.001) or sAg^+/SFL^- subjects (OR=4.287, 95%

CI=2.815-6.526, p<0.001). In subjects with normal ALT (≤40 IU/L) levels, proportions of subjects with actual ALT greater than 20 IU/L in sAg^+/SFL^+ group (44/51) were higher than in sAg^-/SFL^+ group (356/487, p=0.043), sAg^+/SFL^- group (157/223, p=0.022) and sAg^-/SFL^- group (844/1751, p<0.001). Conclusions: HBsAg carriers with sonographic diagnosed fatty liver were similar in metabolic disorders to fatty liver cases without HBsAg, but the former could cause liver damages with higher risks.

P-39

Aquaporin, a kind of membrane channel protein, maybe a new promising therapeutic target for non-alcoholic fatty liver disease

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Non-alcoholic fatty liver disease (NAFLD) is and will continue to be a major liver health issue worldwide in the coming decades. Liver steatosis is present in young patients, it could be a predictive factor of death from cardio-vascular diseases other than hepatocellular carcinoma, as well as of the onset of type 2 diabetes. These considerations strongly indicate the necessity to treat each stage of NAFLD. The therapeutic arena for NAFLD continues to develop and focuses on improving insulin resistence (IR) and decreasing inflammatory microenvironments to prevent or slow the development of non-alcoholic steatohepatitis (NASH). Specific liver drugs for NAFLD are needed in the future research. Recent study demonstrated that aquaporin was a kind of membrane channel protein that facilitated the movement of water through cell membranes. A subfamily of aquaporins, called aquaglyceroporins, coordinated movement of both water and glycerol across cell membranes. Two aquaglyceroporins, adipose-specific aquaporin 7 and liver specific aquaporin 9, might be involved in the pathogenesis of IR and may be reasonable targets of drug development. Aquaporin 7 facilitated the movement of glycerol from adi-

pocytes into the bloodstream, while aquaporin 9 allowed uptake of glycerol into the hepatocyte, which stimulated hepatic gluconeogenesis. In the normal feeding state, insulin inhibited expression of adipose-specific aquaporin 7 and liver-specific aquaporin 9, thereby reducing glycerol export out of adipose tissue and increasing fat accumulation. However, as evidenced by mouse models, IR actually caused an increase in these aquaporins. As a result, increased glycerol was exported from adipocytes to hepatocytes, resulting in increased gluconeogenesis and worsening hyperglycaemia. While, regretfully, the research on human was still blank until now. With mentioned above, we hypotheses that aquaporin maybe a promising therapeutic target for NAFLD in the future.

P-40

Efficacy of pentoxifylline versus pioglitazone intreatment of non alcoholic steatohepatitis

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Background: There is paucity of data on drug therapy in non-alcoholic steatohepatitis (NASH). We compared efficacy of pentoxifylline versus pioglitazone in patients with NASH. Patients and Methods: Forty patients with NASH were randomized to receive pentoxifylline 1200 mg/d or pioglitazone 30 mg/d for six months.Liver function tests, serum insulin, insulin sensitivity, TNF-alfa, adiponectin, leptin levels and liver histology were performed at baseline and after six months of therapy. Results: With six months therapy, there was significant improvement in AST, ALT, serum insulin, insulin sensitivity, TNF-alfa, adiponectin and leptin levels ($p<0.05$) and steatosis and lobular inflammation on liver histology ($p<0.05$). All the parameters showed similar degree of improvement in patients receiving pentoxifylline and pioglitazone. Conclusions: Pentoxifylline and pioglitazone are equally effective in improving liver function tests, metabolic parameters and liver histology in patients with NASH.

Author Index

Abdullah Y *P-15*
Ábel T ***O-42, P-7***
Abonyi M *O-48*
Acott PD *O-20*
Adanez G *P-22*
Agne A *P-4*
Akinli AS *O-18*
Alija A *O-5*
Alireza A *O-57*
Al-Isa A ***O-31***
Altomare E *O-22*
Anahita HR *O-57*
Angelico F *P-2*
Aoun M ***O-17***, O-51
Aponte AM *O-9*
Arunmozhiarasi A *P-27*
Augustine LM *O-27*
Ayala I *P-22*

Babaei H ***P-11***
Baginskaya N ***P-1, P-35***
Bagnato VS *O-24*
Balocco M *P-5*
Bánhegyi G ***O-7***
Bartosz G ***O-3***
Baumert T *O-44*
Bekő G *O-48*
Bellanti F *O-22*
Bellomo RG *O-54*
Berge GM *P-18*
Biasi F ***O-39***
Blázovics A *P-10*
Blonda M *O-22*
Blum HE *O-48*
Boehm BO *O-18*
Bojaxhi E *O-5*
Bresgen N *O-5*
Bressan S *O-14*
Brun P ***O-49***
Bruno D *O-22*

Caldwell S *O-30*
Calvani M *O-54*
Calvani R *O-54*
Campion SB *O-27*
Canbay A *O-50*
Canbay A *P-25*
Caperuto EC *O-19*
Carbonneau MA *O-17, O-51*
Carnevali LC *O-19, O-53*
Carrara P *P-5*
Carruba G ***O-43***
Casas F *O-17*
Castagliuolo I *O-14, O-49*
Castells M *P-22*
Cavallo D *O-14, O-49*
Cavallo MG *P-2*
Cervinkova Z *P-9, P-20*
Chang ML ***P-23***
Chatgilialoglu C ***O-2***
Chau GY ***O-52***
Chen PC *P-8*

Chen YP *P-38, P-39*
Cherkas A *O-55*
Cherrington NJ *O-27*
Chi LS *P-27*
Chiu CT *P-23*
Choi JE *P-14*
Chun TE *P-27*
Connemann BJ *O-21*
Costa Rosa LF *O-19*
Coudray C *O-17, O-51*
Cristol JP *O-17, O-51, P-4*
Crocker JFS *O-20*
Czinner A *O-58*
Csala M ***O-6***
Csihi L *O-48*

Dagnolo S *O-49*
Décordé K ***P-4***
Del Ben M *P-2*
Dienes HP *P-25*

Eckl PM ***O-5***
Eder R *O-53*
Eisenbach C *O-21*
Eldin MG *P-7*
Erickson RP *O-27*
Erman A *P-30*
Erol A *P-30*
Esma A *P-15*

Fajfrová J ***P-6***
Fang SC *P-27*
Farhad HP *O-57*
Fehér J *O-28, O-29,* ***O-33,*** *O-48, P-7, P-21*
Feillet-Coudray C *O-17, O-51, P-4*
Ferreira C *O-24*
Firneisz G ***O-28***
Fisher CD *O-27*
Flechtenmacher C *O-21*
Forni GL ***P-5***
Fouret G *O-17, O-51, P-4*
Fraenkel E ***O-29***
Fraioli A *P-2*
Fülöp P ***O-11,*** *O-41*
Füsun E *P-15*

Galloway TF *P-18*
García-Pérez B *P-22*
Garnol T ***P-9,*** *P-20*
Geldenhuys L *O-20*
Gerken G *P-25*
Ghareeb DA ***P-36***
Ghyczy D *O-28*
Gonçalves DC *O-19,* ***O-53***
Gorshkov IP *P-29*
Guéraud F ***O-10***
Gulgun T *P-30*
Güngör Kanbak ***O-56***
Güvenç G *P-15*

Haenle MM *O-18*
Hafez H *P-36*
Hafize U *P-15,* ***P-30***
Hagymási K ***P-21***
Haihong C *P-32*
Hajifaraji M ***O-57***
Hale A *P-15*
Halmy L *O-32,* ***O-40***
Han Z ***P-33***
Harkanyi Z *O-58*
Hegedüs G *O-46.a*
Hegedűs V ***P-10***

Heuer M ***O-50***
Hillestad M *P-18*
Hlúbik P *P-6*
Holm H *P-18*
Hong SW *P-14*
Horváth E *O-48*
Horváth T *O-48*
Hsiao TJ *P-8*
Hunyady B *O-46.a*
Hur W *P-14*

Ibrahim M ***P-24***
Ilaria B ***P-2***
Ilnitskaya CI *P-1*

Jakovac D *P-26*
Jarčuška P *O-29*
Jordão AA *O-24*
Jullien M *O-17*

Kader HHA ***O-27***
Kaiser GM *O-50*
Kaledin VI *P-1*
Kalovics T *O-58*
Kaminsky YG *P-19*
Kandiah J *P-27*
Karadi Z *O-58*
Karcz WK *P-16, P-17*
Kasapoglu B ***P-3***
Kasper HU *P-25*
Kaštel R *P-31*
Kavandi S *P-11*
Kempler P *O-48*
Khalil AA *P-36*
Khoshnevisasl P *P-11*
Kim JY *P-13*
Kjaer MA ***P-18***
Kollai M *O-48*
Kosenko EA ***P-19***
Kovács A *P-7*
Kratzer W ***O-18***
Krawczykowski D ***P-16, P-17***
Křiváková P *P-9, P-20*
Krogdahl Å *P-18*
Kubálková J *P-31*
Kučera O *P-9,* ***P-20***
Kumar A *P-41*
Kurachi H *O-24*

Lacan D *P-4*
Lancillotti S *O-14*
Lee JG ***P-13***
Lee S *P-13*
Lengyel G *O-28, O-29,* ***O-46****, P-7, P-21*
Lickteig AJ *O-27*
Lima WP *O-19, O-53*
Lin DY *P-23*
Lin YC ***P-8***
Lira FS ***O-19,*** *O-53*
Lombay B ***O-47***
Lotková H *P-9, P-20*
Lyoo KS *P-14*

Mahtab MA ***O-15, O-26***
Manautou JE *O-27*
Mandl J ***O-1***
Mansour NF *P-36*
Marchini JS *O-24*
Martano G *O-5*
Martín-Castillo A ***P-22***
Martines D *O-14, O-49*
Mathé Z *O-50*
Mehta KD ***O-38***

Meisheng W ***P-32***
Melin P *P-17*
Merrell MD *O-27*
Mezei M *P-21*
Michael W *P-27*
Michel F *O-51*
Mihácsi G *P-21*
Mihály Z *P-10*
Min HG *P-13*
Miroshnichenko LA *P-29*
Miseta A *O-46.a*
Miyake Y *P-28*
Molnár L ***P-25***
Montes A *P-22*
Montoliu C *P-19*
Morini S *P-2*
Murphy MG ***O-20***

Nakaguchi T *P-28*
Namiki T *P-28*
Nduwayo L *P-17*
Neuhaus JP *O-50*
Nishino H ***P-12***
Noetel A *P-25*

Odenthal M *P-25*
Oliveira GR *O-24*
Omur T *P-30*
O'Regan P *O-20*
Osztovits J ***O-48***
Ovcharenko NA ***P-37***
Özlem K ***P-15***

Paola B ***O-14***
Pár A ***O-46.a***
Pár G *O-46.a*
Paragh Gy ***O-41***
Paul A *O-50*
Pavlík V *P-6*
Peltekian KM *O-30*
Perepechaeva ML *P-1*
Peterson MR *O-30*
Peterson TC ***O-30***
Piao LS ***P-14***
Pinskyy LL *P-37*
Pivovarova EN *P-1*
Poli G ***O-36***
Pozzilli P *P-2*

Ramos J *P-4*
Remaley AT *O-9*
Remise G *P-15, P-30*
Reshetnikova OS *P-37*
Rey J *P-25*
Rollo T *O-22*
Romano AD *O-22*
Rosa J ***P-26***
Rosa JC *O-19*
Rouanet JM *P-4*
Roušar T *P-9, P-20*
Rőth E *O-46.a*
Ruyter B *P-18*

Sadeghzadeh M *P-11*
Šafka V *P-6*
Saggini R ***O-54***
Sakhuja P *P-41*
Salem MA *P-36*
Sánchez-Polo M *P-22*
Sandelin B *P-25*
Saner FH *O-50*
Sankarankutty AK *O-24*
Sara HT *O-57*
Sárdi É *P-10*

Sarin SK *P-41*
Scheffler M *P-25*
Schmid MM ***O-21***
Schönfeldt-Lecuona C *O-21*
Schuster C ***O-44***
Seelaender MCL *O-19, O-53*
Selmeci L *O-28*
Semen KH *O-55*
Serhiyenko V *O-55*
Serhiyenko O *O-55*
Serviddio G ***O-22***
Setyowati KD ***P-27***
Sharma BC ***P-41***
Shenoy KT ***O-25***
Shi KQ *P-38 P-39*
Siddiqui A ***O-45***
Siems W *O-5*
Signori S *O-14, O-49*
Silva OC *O-24*
Silverio R ***O-23***
Sinđić A *P-26*
Singh RB ***O-16***
Somogyi A *O-28*
Stutz H *O-5*
Sugiyama S ***P-28***
Szabó Gy *O-29*
Szalay F *O-47, O-48*
Szamosi T Jr *O-58*
Szamosi T ***O-58***
Szebeni Á ***O-32***
Szentmihályi K *P-10*
Szollár L ***O-34***

Tamborra R *O-22*
Taşkın R *P-15*
Tavintharan S *P-27*
Tax J *O-48*
Tomsits E *O-58*
Tóth T *O-48*
Trabacca MS *P-5*
Treckmann JW *O-50*
Trencsenyi Gy ***O-37***
Tsay SH *O-52*
Tsumura N *P-28*
Tulassay Zs *O-28*

Upham J *O-20*

Vannuchi H *O-24*
Varga T *O-28*
Vaško L ***P-31***
Vegusdal A *P-18*
Vendemiale G *O-22*
Ventura E *P-4*
Vernadakis S *O-50*
Vesely J ***O-12***
Veysel T *P-30*
Vickers KC ***O-9***
Villa R *P-5*
Vlasov S ***P-29***
Vog IC *O-5*
Volyinkina AP *P-29*
Voncze Á *O-46.a*

Wimmer A *P-7*
Wolf RC *O-21*
Wrutniak-Cabello C *O-17*

Xia C *P-32*
Xie KQ *O-4*
Xin YN *P-39*

Yamaguchi T ***P-34***
Yamamoto S *P-28*

Yamashita AS *O-19, O-53*
Yao Z ***O-8***
Yeh CT *P-23*
Yelisyeyeva O ***O-55***
Yifeng T *P-32*
Yoon SK *P-14*
Yüksel B *P-15*
Zarkovic N ***O-35***
Zeng T ***O-4***
Zheng MH ***P-38, P-39***
Zhu BH *P-38*
Zinchenko OV *P-37*
Zoloedov VI *P-29*
Zucoloto S ***O-24***